Headache

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Headaches are common complaints in children. The International Classification of Headache Disorders, 3rd edition (beta version), defines more than 280 types of headaches. Primary headaches refer to independent conditions that cause pain and include migraine, tension-type headaches (TTH) and trigeminal autonomic cephalalgias (TACs). Several agents are involved in the pathogenesis of headaches. The factors associated with predisposition to atherosclerosis seem to be particularly important from the clinical point of view. The influence of obesity on the incidence of headaches has been well established. Moreover, idiopathic headaches, especially migraine, are thought to be one of the first signs of disorders in lipid metabolism and atherosclerosis. The risk of migraine increases with increasing obesity in children. Another factor that seems to be involved in both obesity and headaches is the adiponectin level.This review presents the current knowledge on the relationship between obesity and adiponectin and primary headaches.

atherosclerosis headache idiopathic headache inflammation child dyslipidaemia paediatric obesity

1. Introduction

Headache is one of the most frequent complaints in primary care practices and a very common condition reported by children, adolescents, and young adults [1][2][3][4]. However, headache phenotypes differ depending on the age group. In the pediatric population, the incidence of headaches increases with age. Conicella et al. observed headaches in 66% of school-age children [5]. The authors demonstrated that 93% of the analyzed children presented a recent onset of headache, whereas medium- and late-onset headaches were reported by 3% and 4% of all patients, respectively [5]. The overall headache prevalence has been reported to be as high as 56% in children under 10 years of age and 91% in early adulthood [3][6]. Additionally, a relationship between gender and the frequency of headaches was observed in pediatric patients. Abu-Arafeh et al. described odds ratio (OR) equal to 1.53 and 1.67 for the prevalence of headache and migraine in female and male patients, respectively [3][6]. During puberty, headaches are more common in girls, whereas in prepuberty, the frequency of headaches is similar in males and females [6][7]. On the other hand, in a large group of adult patients from the USA, migraine was more common among females, but in the case of other severe headaches, no sex difference was observed [2][8]. In some patients, headaches may become a long-lasting health problem as they tend to persist into adulthood. Most patients from Nova Scotia, Canada, having pediatric headaches suffered from headaches in adulthood (i.e., twenty years after diagnosis), whereas 27% were headache-free [9].

Headache classification is a complex issue due to the multi-faceted pathophysiology of this disorder. Possible etiological factors include, inter alia, neuronal, vascular, immunological, and psychological agents [10]. Nowadays, more than 280 headache types and subtypes are defined and categorized in the International Classification of Headache Disorders, 3rd edition, created by the International Headache Society (ICHD-3). The classification consists of four sections: primary headaches, secondary headaches, neuropathies, and appendix [10].

The group of primary headaches includes migraine, tension-type headaches (TTH), trigeminal autonomic cephalalgias (TACs), and other primary headache disorders [10].

The diagnosis of primary headache is strongly related to the patient`s medical history and typical characteristics of headaches described in ICHD-3. A thorough medical history and physical examination are crucial for identifying the etiology [3][10][11].

The treatment of headaches in children and adolescents requires a balanced approach to personalize therapy depending on the kind, frequency, and severity of symptoms as well as the limitations in daily life activities due to pain. The main goal of headache therapy in children is quick resolution with minimal side effects. The multi-faceted effort includes three general stages: lifestyle modification, psychotherapy, and pharmacotherapy [12][13].

A number of risk factors for headache have been demonstrated. Predisposition to atherosclerosis in idiopathic headaches seems to be particularly important from the clinical point of view. Migraine was suggested to be one of the first signs of disorders in lipid metabolism [14]. Elevated lipid concentrations were widely observed in adult migraineurs as well as in a few clinical studies conducted in pediatric patients [14][15][16]. The risk of migraine was also suggested to increase with increasing obesity in children [17][18][19][20].

Recent data suggest that some risk factors for atherosclerosis and platelet aggregation (i.e., brain-derived neurotrophic factor (BDNF), sCD40L (soluble CD40 ligand), serpin E1/PAI I (endothelial plasminogen activator inhibitor), and vascular endothelial growth factor (VEGFO)) may be involved in the underlying processes of idiopathic headaches [21][22][23][24][25][26][27][28][29][30].

The knowledge on the correlation between headaches and factors, which may increase the risk of atherosclerosis, and consequently, premature coronary artery disease, may be of particular importance, especially in the pediatric population.

2. Body Mass Index (BMI)

The available data support the relationship between obesity and headaches in children and adolescents [17][18][19][20][31][32][4][33][34][35][36][37][38][39][40][41][42]. Previous data demonstrated that obesity is associated with more frequent headaches in children and adolescents [17][18][19][20][38][39][41]. According to Pinhas-Hamiel et al., obese girls had a 4-fold increase in headaches compared to lean controls [17]. In the adult population, Peterlin et al. found that obese

individuals had an 81% greater risk of episodic migraine than subjects with normal weight. The risk was particularly high in younger adults (below 50 years of age) and in females [38].

BMI percentile correlated not only with the frequency of headaches, but also with headache-related disability. However, no correlation between obesity and headache severity and duration was found [18][20]. The body mass index of children with headaches correlates not only with the incidence of this ailment, but also with the tendency to relapse and everyday functioning disruptions [18]. Verotti et al. reported that a change of mean BMI from 32.9 kg/m^2 at baseline to 29.9 kg/m^2 after 12 months of an intervention program caused a significant reduction in the headache frequency in obese Italian children and adolescents [43]. Similar data were obtained in the study evaluating the obesity–headache relationship in adolescents (13–18 years). Obese adolescent girls and boys were more likely to have recurrent headaches [43]. In contrast, some authors have reported no correlation between migraine and increased BMI in children [40].

Data on the relationship between obesity and TTH in children are insufficient and controversial, and the obtained results are often contradictory [19][39][40][41]. Pinhas-Hamiel et al. suggested that slightly overweight and obese patients more often fulfilled the TTH criteria than normal-weight children [17][18][39].

The mechanism involved in migraine in obese children is not known and several hypotheses have been suggested. The pathways involved in feeding regulation and those implicated in migraine are consistent in many central and peripheral points, for example, in hypothalamic activation, in the release of adiponectin, serotonin, or other immune modulators and inflammatory neurotransmitters [38][44][45]. Other possible factors involved in the migraine–obesity relationship are lifestyle and habits including migraine medications that could modulate body weight as well as diet and physical exercise of patients [40][44][45][46][47].

3. Adiponectin

Adiponectin is a protein post-translationally modified into various multimers and secreted into the circulation from adipocytes [48]. It shows anti-inflammatory properties and also protects cells from apoptosis. Adiponectin receptors are expressed in the cortex, hypothalamus, brainstem, circumventricular organs, and on the endothelium of the cerebral microvasculature. Several signal transduction mechanisms were found to be activated by adiponectin, of which some are implicated in migraine including nuclear factor kappa beta (NFkβ), AMP-activated protein kinase (AMPK), mitogen-activated protein kinase (MAPK), or endothelial nitric oxide synthase (e-NOS) [49][50]. Previous research demonstrated that obese children had low adiponectin levels, whereas the markers of inflammation and proinflammatory cytokines were elevated [51]. The study by Asayama et al. showed that the levels of adiponectin in obese children were correlated inversely with the visceral adipose tissue area and their serum levels were decreased. Low levels of adiponectin are associated with platelet aggregation as well as proinflammatory cytokine release [52]. The above-mentioned mediators can trigger the following cascade of events: they affect frequency, severity, and duration of migraine attacks, which, especially when repeated, may cause central sensitization, and eventually permanent neuronal damage. Duarte et al. reported significantly higher levels of adiponectin in patients with migraine than in the controls [53]. However, no relation was observed when patients with episodic vs. chronic

migraine as well as migraine patients with aura vs. without aura were compared [53]. On the other hand, a Brazilian study revealed a statistical difference in adiponectin levels between migraine patients and tension-type headaches [54]. The study by Dearborn et al. demonstrated that total adiponectin levels were significantly higher in women compared to men [55].

4. Dyslipoproteinemia

Dyslipoproteinemia, just like obesity, is a common, well-known risk factor for cerebrovascular and cardiovascular diseases [56][57]. Data from large groups of subjects revealed how common the problem of lipid disturbances in children is. In a study by Reuter et al., 42% (out of n = 1243) of healthy Brazilian children and adolescents had dyslipidemia, which was more prevalent in girls than in boys [15]. Almost 20% of Korean children and adolescents aged 10–18 years were reported to have at least one abnormal lipid profile [16].

Elevated lipid levels were observed in adults with idiopathic headaches, but there are only a few small clinical studies showing a relationship between disturbances in lipid levels and migraine in pediatric patients [14][22][58][59][60][61]. A significant positive correlation between the frequency and intensity of migraine and the levels of total cholesterol as well as low-density lipoprotein (LDL) cholesterol was observed in an Italian study. Moreover, in patients treated for migraine prophylaxis, a decreased number and intensity of episodes correlated significantly with a reduction in total cholesterol and LDL levels [14]. Glueck and Bates showed a similar relation between severe migraine headaches and LDL levels in boys with primary and familial dyslipoproteinemias [59]. In a large group of Brazilian adults, the relation between migraine and lipid sub-fraction was assessed [60]. The authors indicated a positive correlation between migraine without aura and the highest tertiles of very-low-density lipoprotein (VLDL) cholesterol in females. On the other hand, in men, a positive association was observed between migraine with aura and the highest tertile of $VLDL_3$ cholesterol [60].

Nevertheless, some authors deny the correlation between lipid levels and the occurrence of primary headaches in children. A large and representative American sample showed no differences in the values of lipid levels by headache status. However, boys with headaches had lower high-density lipoprotein (HDL) levels than asymptomatic patients of the same sex [22].

In contrast, Winsvold et al. reported that total cholesterol levels may be even lower in adults suffering from migraine than in non-migraine controls. In this study, HDL cholesterol showed a similar tendency toward decreased values [61].

Moreover, according to Sacher et al., migraine correlates with an increased risk of ischemic stroke in adult patients in comparison to the healthy population [62][63]. Studies performed in children did not confirm this correlation, but some authors reported a higher prevalence of migraine among young individuals with medical history of stroke, silent infarct-like brain lesions, and cerebrovascular disorders during headache attacks [64][65][66]. The study by Sarecka-Hujar et al. demonstrated that about 40% of children with arterial ischemic stroke had hypertriglyceridemia

[67]. Moreover, the data from the International Pediatric Stroke Study (IPSS) demonstrated that 41% of children with arterial ischemic stroke had elevated levels of TG, whereas 36% of children were dyslipidemic [68].

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