OPIS PRZYPADKU / CASE REPORT
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Loss of appetite and weight loss in an 8-year-old child being treated with methylphenidate. Case report and literature review

Utrata apetytu i spadek masy ciała u 8-letniego dziecka leczonego metylofenidatem. Opis przypadku i przegląd piśmiennictwa

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Summary

Background. Attention deficit hyperactivity disorder (ADHD) is one of the most common psychiatric disorders in childhood, with a prevalence rate of 3–5%. It comprises three main symptom groups: hyperactivity, attention deficit disorder and excessive impulsivity. The disorder begins in early childhood but in many ADHD cases, at least in part, persists into adulthood, and therefore it has to be considered a life-long disorder. It may affect the ability to focus and cause physical and mental restlessness as well as risky behavior. Recommended treatment consists of stimulant administration and behavioral therapy. Several medications are used to treat ADHD. One of them is methylphenidate. This drug has proved efficacy in treating ADHD both in children and adults; however, the therapy with methylphenidate may bring the risk of adverse reactions, some of which are eating disorders such as loss of appetite and/or weight loss. ***Material and methods.*** We describe a case report of an 8-year-old patient who experienced adverse reactions of loss of appetite and subsequently weight loss during the therapy with methylphenidate. ***Results.*** The patient lost five kg of body weight within six months, but due to clinical improvement in ADHD symptoms, treatment with methylphenidate was not cessated. The patient was referred to a dietetic clinic to determine the optimal nutritional plan. ***Conclusions.*** The described case confirms the risk of adverse reactions in the form of appetite and weight loss following the therapy with methylphenidate. *(Farm Współ 2022; 15: 56-61) doi: 10.53139/FW.20221506*

Keywords: attention deficit hyperactivity disorder -ADHD, methylphenidate, adverse drug reactions, eating disorders, loss of appetite, weight loss

Streszczenie

Wstęp. Zespół nadpobudliwości psychoruchowej z deficytem uwagi (ADHD) jest jednym z najczęstszych zaburzeń psychicznych wieku dziecięcego, z częstością występowania 3–5%. Obejmuje trzy główne grupy objawów: nadpobudliwość, zespół deficytu uwagi i nadmierną impulsywność. ADHD zazwyczaj ma swój początek się we wczesnym dzieciństwie, ale w wielu przypadkach, przynajmniej częściowo, utrzymuje się do wieku dorosłego i dlatego należy go traktować jako zaburzenie trwające całe życie. ADHD może wpływać na zdolność koncentracji i powodować niepokój fizyczny i psychiczny oraz zachowania ryzykowne. Zalecane leczenie polega na podawaniu stymulantów i terapii behawioralnej. W leczeniu farmakologicznym ADHD stosuje się kilka leków. Jednym z nich jest metylofenidat. Lek ten jest skuteczny w leczeniu ADHD zarówno u dzieci, jak i u dorosłych, jednak terapia z jego zastosowaniem może nieść ze sobą ryzyko wystąpienia działań niepożądanych, jednymi z których są zaburzenia odżywiania, np. utrata apetytu i/lub masy ciała. ***Materiał i metody.*** Przedstawiamy przypadek 8-letniego pacjenta, u którego w trakcie stosowania metylofenidatu wystąpiło działanie niepożądane w postaci utraty apetytu skutkującej utratą masy ciała. ***Wyniki.*** Pacjent w ciągu sześciu miesięcy utracił pięć kilogramów wagi ciała, jednak ze względu na poprawę kliniczną objawów ADHD nie zaprzestano terapii metylofenidatem. Pacjent został skierowany do poradni dietetycznej w celu ustalenia optymalnego planu żywieniowego. ***Wnioski.*** Opisany przypadek potwierdza ryzyko wystąpienia działania niepożądanego

w postaci utraty apetytu i spadku wagi ciała jako następstw terapii metylofenidatem. *(Farm Współ 2022; 15: 56-61) doi: 10.53139/FW.20221506*

Słowa kluczowe: zespół nadpobudliwości psychoruchowej z deficytem uwagi -ADHD, metylofenidat, działania niepożądane leku, zaburzenia odżywiania, utrata apetytu, spadek masy ciała

Introduction

Attention deficit hyperactivity disorder (ADHD), defined as a persistent neurodevelopmental disorder, is one of the most frequent psychiatric disorders within child and adolescents [1]. The clinical course of ADHD is chronic, with the progressive and constant evolution of symptoms. It usually occurs at age 3 – 4, and the main symptom is hyperactivity. Later, at 5 – 6 years of age, hyperactivity also begins to be accompanied by inattention. ADHD is a clinically heterogeneous syndrome characterized by developmentally inappropriate hyperactivity, mood lability, inattentiveness, irritability, increased impulsivity and even aggressiveness [2-3]. The essence of these symptoms is related to their coexistence, which in the medical sense makes them a symptom complex. Many children have problems with excess energy, but the hyperactivity syndrome is only mentioned when these symptoms are disproportionate to the age and level of development of the child, and also become a source of failure, disrupt the functioning at home and school, and affect the child's learning and development. These people show difficulties in purposeful activities, planning activities and selecting stimuli [4]. There is no single risk factor that is necessary or sufficient to cause ADHD. However, prenatal complications, an episode of hypoxia, prematurity, nutritional deficiencies, and lack of adequate socialization, environmental and epigenetic factors, and genetic predispositions (the disorder is hereditary) are considered of great significance [2]. Genome-wide association studies (GWAS) have shown that ADHD's heritability is partly due to a polygenic component comprising many common variants, each having small effects or rare insertions or deletions. Interestingly, childhood and adult or persistent ADHD can be genetically distinct subtypes [5-6]. This disorder impairs multiple aspects of life to a great extent. It may affect concentration, lead to mental and physical restlessness and risky behavior [7]. ADHD can increase the risk of other psychiatric disorders (including affective disorders, defiant, antisocial personality disorder, self-harm, substance misuse, placing a considerable burden on society and family), educational and occupational failure, unemployment, unsuccessful relationships, accidents, criminality, social disability and addictions throughout an individual's lifetime [3, 8]. As the causation of ADHD is multifactorial, the disorder is heterogenetic, which is reflected in its extensive psychiatric comorbidity, multiple domains of neurocognitive impairment and the wide range of structural and functional brain anomalies associated with it. ADHD affects 3 – 5% of children worldwide [8,9]. Around 50 – 80% of people with ADHD have symptoms that continue into adolescence, and in about 40%, symptoms continue into adulthood [2]. A meta-analysis from 2017 considering data from twenty countries has estimated that the worldwide prevalence of ADHD in adults was 2.8%, ranging from 0.6 to 7.3%, depending on the financial situation of a given country [10]. The prevalence of persistent adult ADHD (with a childhood-onset) and symptomatic adult ADHD (regardless of a childhood-onset) decreased with advancing age. In 2020 the prevalence of persistent adult ADHD was 2.58%, and that of symptomatic adult ADHD was 6.76%, translating to 139.84 million and 366.33 million affected adults worldwide [3]. Similarly to younger individuals, ADHD in older adults is accompanied by increased rates of mood and anxiety symptoms, general health problems, conflicts, divorce, loneliness, and a lower income [9]. For children, diagnostic and treatment services are available throughout most of Europe. ADHD is diagnosed based on the observation of behavioral symptoms. Following the DSM-5 (the Diagnostic and Statistical Manual of Mental Disorders, 5th edition), the major symptoms of ADHD are divided into symptoms of inattention (11 symptoms) and hyperactivity/impulsivity (9 symptoms). Although comorbidity with other mental disorders is common, ADHD should be excluded if other mental disorders can better explain the behavioral symptoms (e.g., psychotic disorder, mood or anxiety disorder, personality disorder, substance intoxication, or withdrawal) [1]. Other methods that may be helpful in the diagnosis of ADHD are, e.g. examination of motor activity using Doppler radar or performing a quantitative EEG

(QEEG) [11-13]. In line with the international guidelines, treatment of ADHD should follow a multimodal approach, combining behavioral and pharmacological treatment. Pharmacological treatment of ADHD – as with other psychiatric disorders in children and adults – is symptomatic. The drug of the first choice and the most widely used treatment for ADHD in Europe is methylphenidate (MPH) [14]. However, its use may be accompanied by several side effects, including decreased appetite and abdominal pain.

Case report

We describe a case of an 8-year-old boy, 135 cm tall, weighing 36 kg (BMI = 19.75 kg/m^2) with ADHD, treated with methylphenidate hydrochloride in an initial dose of 5 mg/day, which was increased to 10 mg/day after one week as recommended by a physician specializing in the treatment of childhood behavior disorders. Psychological and educational activities were also included in the treatment of the disorder. A baseline assessment of the patient's cardiovascular system (blood pressure and heart rate) and careful height and weight measurements were performed prior to initiating the therapy with methylphenidate. The dosing regimen was set to the recommended 5 mg twice a day (with breakfast and lunch) and reduced the patient's hyperactivity and impulsiveness. During the third week of treatment, the patient began to experience a loss of appetite. After three months of treatment, the follow-up visit revealed a weight loss by 3 kg, and then by 5 kg after six months. The observed clinical improvement in long-term treatment resulted in referring the patient to a dietary clinic. The boy was recommended to use a properly balanced diet that covers the demand for nutrients necessary for proper growth and development.

Discussion

Methylphenidate (MPH) has been an FDA-approved CNS (Central Nervous System) stimulant for treating attention deficit hyperactivity disorder (ADHD) in children (at least six years of age) and adults since the 1990s. Apart from that, MPH is used as a second-line treatment for narcolepsy in adults. There are also few off-label uses, which include treatment for fatigue in patients with cancer, refractory depression in the geriatric population, apathy in Alzheimer's disease, and enhancing cognitive performance (it is a federally controlled Schedule II substance as it can be abused as a cognitive enhancer); however, the MPHs' efficacy for these uses varies from limited to moderate [15,16]. MPH has a more noticeable effect on the psyche than on motor activity. Methylphenidate belongs to a class of piperidine-derived compounds and is a racemic mixture comprised of the D- and L-threo enantiomers (the D-threo enantiomer is more pharmacologically active) [17-18]. The mechanism of the therapeutic effect in ADHD is not entirely clear, but it focuses on creating a classic stimulant effect within the CNS, mainly in the prefrontal cortex. Methylphenidate exhibits a multimodal mechanism of action. The drug's primary mechanism of action involves working as a dopamine and noradrenaline reuptake inhibitor. It results in increased release of these monoamines into the synaptic cleft. MPH increases extracellular dopamine in the striatum, nucleus accumbens, and prefrontal cortex. Due to the increased neurotransmission of dopamine and noradrenaline, methylphenidate appears to increase the firing rate of neurons, influencing the prefrontal cortex (responsible for executive function). The rewarding and therapeutic effects of methylphenidate depend on both the dopamine D1 and D2 receptor subtypes. It is suggested that activity at D1 receptors and noradrenergic receptors in the prefrontal cortex may have particular relevance to the therapeutic activity of MPH. In contrast, D2 receptors might be more involved in its rewarding effects. Considering the rewarding properties of this drug and attenuating these effects, the mu opioid receptor (MOR) has been shown to be a potential target. It has also been shown to redistribute the vesicular monoamine transporter-2 (VMAT-2) selectively. In addition, MPH is also a weak agonist at the serotonin 1A receptor 5HT1A, contributing to increased dopamine levels. As methylphenidate increases dopamine levels (by direct inhibition of the dopamine transporter and via indirect regulation of the vesicular monoamine transporter 2), it can be a neuroprotective agent in certain conditions like Parkinson's disease (which involves loss of dopaminergic neurons). All these mechanisms of MPH's action help improve function and experience several benefits such as improved attention and reduced hyperactivity-impulsivity [15,18,19].

Methylphenidate chemically derives from phenethylamine and benzylpiperazine and is metabolized to ritalinic acid through hepatic de-esterification via liver carboxylesterase 1 (CES1A1). MPH is mainly administered orally in the form of tablet or capsule

(in immediate (IR), extended (XR or ER), and sustained formulations), and less commonly as a transdermal patch and the dosages range from 5 mg to 60 mg (the dose of 72 mg should not be exceeded) [15]. After oral administration, MPH is quickly absorbed from the gastrointestinal tract; food does not affect the total absorbed amount of the drug. In standard release form, the peak plasma concentration is 1-2 h. In extended-release preparations, the concentration profile of the active substance in plasma is two-phase: the first release phase occurs after 1-2 h following administration and the other – after the next few hours (~4.7 h) [15,17]. It is not entirely known how methylphenidate may affect plasma concentrations of medicinal products administered simultaneously. Therefore, it is recommended to maintain caution in using MPH with other medications, especially those with a narrow therapeutic range. Methylphenidate is not metabolized by cytochrome P450 in a clinically significant range. The activators and inhibitors of cytochrome P450 seem to have no significant impact on methylphenidate pharmacokinetics. D-and L-methylphenidate enantiomers also do not inhibit cytochrome P450 1A2, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A. Considering the interactions of methylphenidate with other medications, it may inhibit the metabolism of coumarin anticoagulants (warfarin), anticonvulsant drugs (e.g., phenobarbital, phenytoin, primidone) and some antidepressants (tricyclic antidepressants and SSRIs) [15,17,20].

Methylphenidate may induce several adverse effects. The most prevalent are headaches, irritability, nervousness, mood swings/lability and insomnia. Concerning CNS, the therapy with MPH may bring dizziness, headache, tics, restlessness/akathisia, tachycardia, and palpitations in case of cardiovascular systems; nausea, vomiting, dry mouth, decreased appetite, weight loss and abdominal pain regarding gastrointestinal reactions. In children on long-term treatment with MPH, growth retardation (decreased height, weight, and bone marrow density) has been observed. Therefore, in case of insufficient height or weight gain, the discontinuation of treatment with this drug should be considered. Apart from that, cases of sudden death have been reported in both children and adults with a pre-existing structural cardiac abnormality. In adult individuals, stroke and myocardial infarction have also been observed. Thus, in patients with a structural cardiac abnormality, cardiomyopathy, or arrhythmias, it is advisable to avoid methylphenidate [15,17].

Concerning the gastrointestinal adverse effects, it should be mentioned that MPH has been reported to exert the anorexigenic effect. According to Brown et al., about one third of children and adolescents treated with therapeutic stimulants reports decreased appetite (in most patients, this effect is transient or clinically insignificant) [21]. Methylphenidate has been reported to increase the risks of decreased appetite, weight loss, and abdominal pain in children and adolescents with ADHD [22]. In a study by Roche et al. that aimed to report the efficacy and safety of MPH on ADHD in children with Down syndrome, loss of appetite was observed in 29% of patients [23]. A work by Osland et al., which included eight randomized controlled trials with 510 participants- children with both ADHD and a chronic tic disorder- and aimed to assess the effects of pharmacological treatments for ADHD, revealed that therapy with methylphenidate was associated with appetite suppression or weight loss [24]. Various aspects of methylphenidate adverse reactions in children with attention deficit-hyperactivity disorder were also scrutinized by Khajehpiri et al. Seventy-one patients (25 girls and 46 boys) with ADHD under methylphenidate were screened regarding all subjective and objective adverse drug reactions of this drug during the six months period- it occurred that 74.3% of children developed anorexia [25]. There are also suggestions that the cessation of long-term treatment with MPH could be responsible for a rebound effect, resulting in appetite enhancement and weight gain. A good example comes from a report of a male patient with childhood ADHD, who discontinued MPH treatment at the age of 11 years and was not followed-up until the age of 16. Within one year of MPH cessation the patient's body mass index increased by five points (while the symptoms of ADHD were re-emerging); he developed DSM-5 criteria for eating disorders [26]. Although it is considered an adverse reaction, the weight loss induced by MPH in some cases may be of benefit. Horne et al. performed an analysis including children with a history of brain tumor and hypothalamic obesity receiving methylphenidate (10-60 mg/day) for hypothalamic obesity. Children were evaluated for BMI trajectory before and after methylphenidate start. There was a 69.9% reduction in the median slope of BMI change following methylphenidate treatment; 92% of patients had a reduction in the slope of their BMI change on MPH treatment – stimulant therapy with MPH occurred effective for the treatment of hypothalamic obesity as it reduced and sustained BMI change [27].

Height and weight gain suppression in children caused by methylphenidate usually occur in the first year, and it may disappear or attenuate slowly, over time. Moreover, body mass is affected earlier, whereas height is affected later and at higher doses of the drug (and more in individuals who started MPH at prepuberty). These growth deviations may be dangerous as they lead to metabolic changes in bone structure and alterations in related blood biochemistry parameters [28]. The mechanisms by which methyphenidate induces adverse effects ranging from loss of appetite to anorexia are not entirely clear. One of the most probable mechanisms is MPHs' action on the dopaminergic system. Methylphenidate increases dopamine signalling in synapses by blockade of dopamine reuptake into the pre-synaptic terminal, increasing availability of pre-synaptic dopamine D2 autoreceptors and activation of D1 receptors on the postsynaptic neuron. The intracerebral activity of methylphenidate might be incriminated in the dysregulation of appetite due to eliciting a reward response, normally induced by food intake, therefore suppressing the normal drive to eat [29]. Another theory is that MPH may stimulate the disgust sensation generated after the activation of the insular lobe by this drug [30]. The objective of an investigative study by Sahin et al. was to explore whether the use of MPH relates leptin, ghrelin, adiponectin, and brain-derived neurotrophic factor (BDNF) and to evaluate the relationship between these biomolecules and methylphenidate-related weight loss in thirty ADHD patients (plus twenty healthy controls). The levels of leptin, ghrelin, adiponectin and BDNF were measured at baseline and after two-month treatment in both groups. At baseline, levels of the molecules were similar in the ADHD and control groups. After a 2-month treatment period, 70% of individuals from the ADHD group experienced the loss of appetite, whereas weight loss occurred in 66.7% of people from this group. It also occurred that leptin and BDNF were not associated with poor appetite and/or weight loss due to MPH treatment. However, ghrelin and adiponectin might play a role in underlying neurobiological mechanisms of MPH-related appetite or weight loss [31].

Conclusion

ADHD is one of the most commonly diagnosed and treated childhood mental disorders. Children diagnosed with ADHD have difficulties with concentration and are often hyperactive and impulsive, making it difficult to achieve good results in school. Their behavioral problems can also affect their ability to build good relationships with family and friends. Methylphenidate is the most commonly prescribed and efficacious drug in the treatment of children and adolescents with ADHD. However, methylphenidate's mechanism of action is pretty complex. Considering factors such as individuals' drug metabolism, other diseases, and concomitant drugs, patients should be aware of possible adverse reactions. The described case of an 8-year-old boy, who experienced the loss of appetite and weight, confirms the risk of adverse reaction in the form of eating disorder following the treatment with MPH and indicates how important it is to observe the juvenile patients, to prevent more severe consequences.

Conflict of interest
None

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