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Case Report

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Transient Hematuria Associated with Modified-Release Methylphenidate

Modifiye Salınımlı Metilfenidat ile İlişkili Geçici Hematüri

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder that often requires pharmacological treatment, with methylphenidate (MPH) being a first-line therapy. While generally well-tolerated, MPH is associated with a range of side effects, some of which are rare and poorly understood. This article presents a case of hematuria in a pediatric patient who is using MPH, aiming to explore the potential link between MPH use and hematological side effects, such as bleeding. A 7-year-old female patient with ADHD and conduct disorder developed hematuria following an increase in the dose of modified-release MPH. The hematuria resolved after discontinuation of the modified-release formulation and switching to immediate-release MPH. Extensive medical evaluation revealed no other underlying causes for the hematuria. Although rare, hematological side effects, including hematuria, can occur in patients using MPH. The potential mechanisms underlying these effects may involve dopamine-induced changes in platelet aggregation, possibly contributing to bleeding or thrombocytopenia. While only a few cases have been reported, the connection between MPH and bleeding diatheses remains unclear. Further clinical studies are needed to explore the pathophysiological mechanisms of these rare side effects. MPH induced hematuria, although rare, should not be overlooked, particularly in patients who have difficulty expressing their symptoms. A better understanding of the mechanisms and regular monitoring of patients receiving MPH treatment may help identify and manage this rare side effect more effectively.

Keywords: Attention deficit hyperactivity disorder, methylphenidate, hematuria

ÖZ

Dikkat eksikliği/hiperaktivite bozukluğu (DEHB), yaygın bir nörogelişimsel bozukluktur ve tedavisinde genellikle metilfenidat (MPH) ilk tercih edilen ilaçtır. Genellikle iyi tolere edilse de MPH bazı yaygın yan etkilerle ilişkilidir ve bunlardan bazıları nadir olup tam olarak anlaşılmamıştır. Bu makale, MPH kullanımına bağlı olarak gelişen hematuri olgusunu sunmakta ve MPH hematolojik yan etkileri, özellikle kanama ile olan olası bağlantısını incelemeyi amaçlamaktadır. Yedi yaşında DEHB ve davranım bozukluğu tanılı bir kız çocuk, modifiye salım MPH dozunun arttırılmasının ardından hematuri gelişmiştir. Hematuri, modifiye salım formülasyonu kesildikten ve kısa etkili MPH geçildikten sonra düzelmiştir. Yapılan kapsamlı tıbbi değerlendirmede, hematuriye yol açabilecek başka bir altta yatan neden bulunmamıştır. Her ne kadar nadir olsa da MPH kullanımında hematolojik yan etkiler, özellikle hematuri görülebilir. Bu etkilerin olası mekanizmaları, dopaminin platelet agregasyonunda yarattığı değişikliklerle ilişkilendirilebilir ve bu durum kanama veya trombositopeniye yol açabilir. Ancak, MPH kanama yatkınlıklarıyla olan bağlantısı hala netleşmemiştir. Bu nadir yan etkilerin patofizyolojik mekanizmalarını araştırmak için daha fazla klinik çalışmaya ihtiyaç vardır. MPH neden olduğu hematuri, nadir olmasına rağmen, özellikle şikayetlerini ifade etmekte zorlanan hastalarda göz ardı edilmemelidir. Bu nadir yan etkinin mekanizmalarının daha iyi anlaşılması ve izlenmesi, bu yan etkinin daha etkin bir şekilde yönetilmesine yardımcı olabilir.

Anahtar Kelimeler: Dikkat eksikliği hiperaktivite bozukluğu, metilfenidat, hematüri

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD, as defined by the DSM-5) and hyperkinetic disorder (HKD, as outlined in the ICD-10) refers to a developmental condition that begins in childhood and persists for at least six months across various contexts. This condition is characterized by three main symptoms: inattention, impulsivity, and motor restlessness (1). While inattention and poor planning skills are often persistent and may negatively impact daily functioning, impulsivity also frequently continues. Motor restlessness, on the other hand, may decrease from adolescence onward, with overt hyperactivity being replaced by an internal sense of restlessness and a constant urge to move (2).

ADHD is a condition that is often overlooked and insufficiently treated (3). Studies have shown that, when ADHD is left untreated, there is an increase in risky behaviors, more frequent accidents, more prominent relationship issues, and a higher prevalence of substance abuse behaviors in individuals (4,5). Particularly, these individuals face significant challenges in social and academic domains, which increases the risk of developing psychological issues such as depression and anxiety. In the long term, this condition can negatively affect individuals' quality of life and reduce their workforce participation (6). According to the guidelines published by the National Institute for Health and Care Excellence in March 2018 and updated in September 2019, pharmacological treatment is recommended for children aged 5 and older, as well as adolescents, when ADHD symptoms persist in at least one area of daily life (e.g., social, academic, or interpersonal relationships), despite environmental adjustments (7).

Methylphenidate (MPH) is ADHD. It has been shown to result in significant improvements in 70% to 80% of individuals with ADHD (8,9). However, MPH is associated with common side effects such as insomnia, headaches, exacerbation of tics, irritability, anxiety, appetite loss, abdominal discomfort, and weight loss. Additionally, although rarer, more severe adverse effects, including psychotic episodes, seizures, tachycardia, weight gain, and drowsiness, have also been reported in the literature (10,11). This article aims to present a case of hematuria, which is suspected to be related to the use of MPH, in light of existing research.

CASE REPORT

A 7-year-old female patient presented to the Child and Adolescent Psychiatry Clinic at AUniversity of Health Sciences Türkiye, Adana City Training and Research Hospital with complaints of irritability, hyperactivity, dangerous behaviors, and self-mutilation. According to information from her parents, the patient was harming others at home and school, becoming angry when things did not go as she wanted, feeling restless shortly after starting to study, and exhibiting a high level of lack of attention, leading to falls and injuries. Additionally, she frequently lost or forgot her belongings at school. Following clinical evaluation and psychometric tests, the patient was diagnosed with ADHD and conduct disorder (CD). Treatment was initiated with 10 mg of modified-release MPH and 1 mg of risperidone, which resulted in significant improvement in her symptoms. MPH was supplemented with risperidone, an atypical antipsychotic, to address the comorbidity of CD.

However, after two weeks, the patient's symptoms began to flare up again, and the modified-release MPH dose was increased to 20 mg/day. After two months of treatment with 20 mg/day modified-release MPH the patient reported noticing bloody stains on her underwear, blood in her urine, and a burning sensation during urination. The complaints were absent during weekends when only risperidone 1 mg was administered without the modified-release MPH. No food or medications were consumed that could cause red urine.

The patient underwent a comprehensive medical evaluation, which included urinary system ultrasonography, X-rays, and detailed urine and blood tests. No underlying pathology was found. Laboratory tests conducted during the pediatric consultation showed no signs of infection, such as elevated white blood cells or C-reactive protein levels. Urine microscopy revealed the presence of erythrocytes, but no leukocytes were found, and no bacterial growth was observed in the urine culture.

The patient was referred to the pediatric hematology clinic. In the peripheral smear, erythrocytes appeared normochromic-normocytic, and the platelet count was within the normal range. No abnormalities were found in the bleeding disorder tests. During the pediatric nephrology consultation, kidney function tests were normal. The urinary ultrasound showed normal positioning of both kidneys bladder wall thickness, and the findings were within normal limits.

The patient had no history of hypertension or bleeding disorders, and she had not recently used non-steroidal anti-inflammatory drugs, warfarin, or any antiplatelet agents. No physical causes that could explain the urinary bleeding, such as genital trauma, surgery, or infection, were identified. When the modified-release MPH was discontinued and replaced with 10 mg immediate-release MPH, no further issues were observed.

DISCUSSION

Existing literature and clinical observations indicate that MPH is generally well tolerated in the treatment of ADHD. Most of the common side effects are temporary and do not require discontinuation of treatment (12). To the best of our knowledge, only one case of hematuria associated with MPH use in children and adolescents with ADHD has been reported, which occurred after an increase in the dose of Osmotic Release Oral System-Methylphenidate Hydrochloride (OROS-

MPH) (13). However, there are few reports of hematological side effects and bleeding, and a definitive causal relationship has not been firmly established (14).

Some case reports suggest a potential link between MPH and thrombocytopenia (15). In a case reported by Coskun and Adak (16) excessive and frequent menstruation occurred in an adolescent girl with ADHD while using OROS-MPH. Regarding the potential mechanisms of bleeding associated with MPH, it is plausible that in this case, OROS-MPH could have triggered a bleeding diathesis, such as thrombocytopenia, which may have led to bleeding. Another study hypothesized that MPH-induced thrombocytopenia might be related to peripheral platelet destruction. Under normal conditions, dopamine acts as a co-agonist for adenosine diphosphate (ADP)-induced aggregation, exerting a pro-thrombotic effect. However, prior studies have shown that at elevated dopamine levels, it acts as an anti-thrombotic agent. We propose that the increased dopamine levels, induced by MPH, could contribute to an anti-thrombotic state, which might result in hematuria (17-19).

It is well established that MPH enhances dopaminergic transmission by inhibiting dopamine transporters (20). The various effects of dopamine on platelet aggregation have been documented in earlier studies. These include dopamine-induced platelet aggregation at micromolar concentrations, enhanced ADP-induced platelet aggregation, and inhibition of epinephrine-induced aggregation (21). In another case report, it was noted that a decrease in platelet count occurred after the use of MPH, which led to a switch to atomoxetine treatment. Subsequently, the platelet count returned to baseline levels (22). Monozygotic twin sisters, experienced menorrhagia after starting MPH, despite their platelet levels being normal. The condition improved after they discontinued the medication, suggesting a possible connection between MPH and a genetic predisposition rather than an idiosyncratic reaction (23).

In our case, hematuria was observed following the increased doses, of long-acting modified-release MPH, and it did not recur when the medication was discontinued or when switched to the short-acting form, IR- MPH. Furthermore, no other medical causes were identified during the investigation. In this context, we may conclude that the hematuria was likely associated with modified-release MPH treatment, similar to the previously reported case (24).

CONCLUSION

Although there are limited reports in the literature regarding MPH causing hematuria or bleeding, this side effect should not be overlooked, especially in patients who have difficulty expressing their complaints. Further clinical studies are needed to better understand and monitor the mechanisms of this rare effect. Additionally, research on the hematological side effects of MPH could help in developing safer treatment strategies.

Ethics

Informed Consent: Written assent from the patient and consent from his parents/guardians were received for publication of this case report.

Footnotes

Author Contributions

Surgical and Medical Practices: C.K., Y.K., S.G., Concept: C.K., Y.K., S.G., Data Collection or Processing: C.K., Y.K., S.G., Analysis or Interpretation: S.G., Literature Search: C.K., Y.K., S.G., Writing: C.K.

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