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EDİTÖRE MEKTUP / LETTER TO THE EDITOR

Modified-release methylphenidate-induced Raynaud's phenomenon in an adolescent with attention deficit hyperactivity disorder

Dikkat eksikliği hiperaktivite bozukluğu olan bir ergende modifiye salımlı metilfenidat kaynaklı Raynaud fenomeni

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To the Editor,

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder commencing before the age of 12 years and characterized by developmentally inappropriate inattention, hyperactivity, and/or impulsivity symptoms[1]. Stimulants such as methylphenidate (MPH) are safe drugs used as first-line therapy for children with ADHD[2]. Psychostimulants may be associated with vascular problems[3,4,5,6]. Raynaud's phenomenon (RP) is a peripheral vasculopathy potentially associated with connective tissue diseases characterized by recurring reversible vasospasm attacks triggered by cold and emotional stress[7]. Several cases have been published involving RP observed with MPH[8,9]. The present case discusses a 14-year-old girl with ADHD who experienced RP with the addition of 10 mg modified-release MPH during 27 mg osmotic release (OROS)-MPH therapy, but not during 36 mg OROS-MPH therapy.

NA, a 14-year-old girl, first presented to us of her own volition, in the company of her parents, with symptoms of inability to concentrate in class, hyperactivity, and inadequate academic performance. The patient and her parents of the case gave verbal and written consent, and the case gave assent for publication. History taken from the family revealed that these problems had been present since elementary school. ADHD was diagnosed based on psychiatric evaluation and the Conners parent and teacher rating scales. The patient was started on 27 mg/day long-acting MPH (OROS-MPH). At evaluation one month subsequently, partial response was determined, and treatment was increased to 36 mg/day OROS-MPH, and no side-effects were observed. At subsequent re-evaluation, a 40% decrease in the ADHD symptoms was observed, with no side-effect other than lack of appetite. Since the patient had not benefitted sufficiently from the 36 mg/day OROS-MPH dosage and was also unable to tolerate the suppression of appetite side-effect, the dosage was modified to 27 mg/day OROS-MPH and 10 mg/day modified-release MPH. The patient was re-evaluated after one month. Her history revealed that her ADHD symptoms had improved by 60-70% and that she had benefited significantly from the medication. However, cold, chill, cyanosis, pallor, and finally erythema symptoms had appeared in her hands. Physical examination revealed cold, chill, first pallor and later erythema, and delayed capillary vessel filling in the patient's hands. However, no ulceration or necrosis were present. The symptoms emerged 1-2 hours after each dose of medication and persisted for 6-7 hours. The patient's family also confirmed these symptoms. The pediatric rheumatology department was consulted. RP was suspected, and no systemic finding was detected. The patient's blood tests, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor (RF), and anti-nuclear antibody (ANA) were negative. It was learned that she did not use any medicine, herbal product or

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substance. She also had no history of any rheumatological disease or allergy. There was no history of connective tissue disease in the family. Both forms of MPH were discontinued, and the symptoms resolved. She was again started on OROS-MPH 27 mg/therapy, and no recurrence of RP was observed. Modified-release MPH at 10 mg/day was added to the treatment while the patient was using 27 mg/day OROS-MPH, and recurrence of RP was then observed. The patient scored 9 on the Naranjo side-effect scale. These symptoms were evaluated as being related to modified-release MPH. Since the patient was unable to tolerate this adverse effect, her treatment continued with atomoxetine. No cold, chill, pallor, or erythema were observed in the patient's hands at subsequent follow-ups.

This case describes a 14-year-old girl experiencing RP with the addition of 10 mg modified-release MPH during 27 mg OROS-MPH therapy, but with no RP during 36 mg OROS-MPH therapy. RP recurring with modified-release MPH therapy and entirely resolving following discontinuation suggests a causal effect. Our patient experienced RP while receiving OROS-MPH 27 mg/day and 10 mg modified-release MPH, but not with 27 mg OROS-MPH. This suggested a side-effect associated with this form of MPH. Her Naranjo probability score was 8, indicating a probable adverse reaction[10]. In the present case, RF resolved when the drug was discontinued but, in contrast to other cases, recurred when the drug was resumed.

There are a limited number of cases in the literature concerning the relationship between RP and psychostimulants such as modified-release methylphenidate, OROS-MPH and dextroamphetamine in children and adolescents[8,9,10,11]. In cases, A significant association was observed between presence of RP and previous or current stimulant use for the treatment of ADHD. Syed et al. described two girls with ADHD, aged 10 and 12, developing RP during MPH therapy[10]. Yu et al. also reported four children with ADHD experiencing vascular changes in their hands and/or feet while using psychostimulants[8]. In the cases reported by Syed et al., Yu et al., Meridor et al., and Ferahkaya et al. methylphenidate was stopped and not resumed subsequently. RF was therefore observed again after resumption of the medication [8,9,10,11]. All these findings suggest a relationship between RP development and stimulants. However, Meridor et al. did not consider the temporal relationship between the onset of RP and current stimulant use[12].

MPH causes an increase in extracellular dopamine and norepinephrine levels in neurons by inhibiting dopamine and norepinephrine transporters. In addition to its central effects, increased extracellular norepinephrine also can lead to a rise in catecholamines in the peripheral vascular system, resulting in vasoconstriction and ischemia[13,14,15]. Exacerbation of symptoms may occur in patients with underlying vascular disease after starting MPH therapy due to its sympathomimetic effects[15].

There may be differences in terms of RP development between different forms of MPH. Although no RP developed during OROS-MPH use in the present case, RP findings were present with the modified-release form of MPH. However, no similarity or difference was reported in any of the previous reports. To the best of our knowledge, this is the second report to the effect that the vascular side-effects of MPH may vary depending on the type of MPH[9].

Physicians should be aware of these potential skin changes when prescribing psychostimulants for the treatment of ADHD. Since RP can lead to severe complications such as digital gangrene, clinicians must be aware of this potential adverse effect of MPH in adolescents with ADHD[16].

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