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Methylphenidate-induced Orofacial Dyskinesia: Report of Two School-age Boys in Taiwan

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Abstract Methylphenidate (MPH) is a stimulant medication commonly prescribed in the management of attention-deficit/hyperactivity disorder. The possible adverse effects of MPH include decreased appetite, sleep disturbance, weight loss, headache, abdominal pain, anxiety and irritability. Some case reports have indicated that orofacial dyskinesias could develop under MPH administration. We report two cases of MPH-induced orofacial dyskinesia in Asian patients. The first patient took MPH 10 mg once daily for one week and developed lip-smacking and lip-biting with bleeding. The second patient developed oral-buccal dyskinesia immediately after he took one 10 mg dose of MPH. The purpose of this case report is to emphasize the importance of clinicians paying close attention to the risk of orofacial dyskinesia related to MPH at any point in the treatment, even when patients are receiving standard doses of this agent.

Key words ADHD; Movement disorder; Psychostimulant

Introduction

Attention-deficit/hyperactivity disorder (ADHD), which occurs in 3% to 10% of children and adolescents, is a common neurodevelopmental disorder. The core symptoms of ADHD include inattention, hyperactivity, impulsivity and impairments in social and academic functioning. Methylphenidate (MPH) is a stimulant medication commonly prescribed in the management of ADHD. The efficacy and safety profiles of MPH have been well-established. Most adverse events of MPH, including decreased appetite, sleep disturbance, weight loss, headache, abdominal pain, anxiety and irritability, are transient and can be alleviated through dose adjustment.[1] Another adverse event, orofacial dyskinesia, involves involuntary repetitive movements of the mouth and face; they usually occur in patients who receive long-term treatment with antipsychotic drugs. It is noteworthy that several case reports, most from Western countries, have indicated that orofacial dyskinesia could develop under MPH administration.[2-6] Such a side effect is commonly seen in children who are receiving combination of medications (e.g. MPH plus neuroleptics or MPH plus anti-epileptic medications) or children with ADHD as well as developmental delay.[6] However, orofacial dyskinesia has also been observed in a healthy toddler who took MPH accidentally.[4] It represents that MPH ingestion can affect a wide spectrum of children – from healthy children to children with multiple developmental disabilities. Nevertheless, MPH-induced orofacial dyskinesia has not been reported yet in Asian populations. Herein, we report two school-age boys in Taiwan who developed transient orofacial dyskinesia following the administration of MPH.

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Case Report

Patient A is a 7-year-old male second-grade student in elementary school. His birth history was generally smooth, and no delay in developmental milestones was observed.

There was no history of head trauma, epilepsy or other neurological diseases. Nevertheless, this boy had congenital multiple syndactyly and underwent operation at 1 year old and 4 years old. He suffered from a short attention span, hyperactivity, impulsivity and excessive talking were observed during class. At age 7, he had his first evaluation at a child psychiatric outpatient department, and ADHD was diagnosed. Psychological testing using the Wechsler Abbreviated Scale of Intelligence (WISC-IV) showed that he had normal intelligence (full intelligence quotient: 85). The patient was treated with 10 mg of short-acting MPH (MPH-IR) once daily. He took the medicine regularly, and no other drug was used simultaneously. One week later, lip-smacking and lip-biting with bleeding suddenly developed 60 minutes after MPH-IR administration. There was no abnormality in movement other than in the oral-facial area. Throughout this period, he had clear consciousness and denied any psychological distress. The involuntary movements spontaneously improved during the evening of the same day. He then stopped the medication. No other abnormality was noted during further follow-up at the outpatient department.

Patient B is a 9-year-old third-grade student in elementary school. He was born at full-term and without any perinatal insult. He presented with global developmental delay and had his first psychiatric assessment at 39 months old. Psychological testing using the Chinese Child Developmental Inventory revealed that he had delays in speech, motor and social development. Autism spectrum disorder (ASD) was highly suspected. In addition to ASD symptoms, ADHD-like symptoms (e.g., poor sustained attention, impulsivity and hyperactivity) were observed at age 9. Psychological testing using the WISC-IV revealed borderline intelligence, with a full intelligence quotient of 71. An additional diagnosis of comorbid ADHD was made. MPH-IR was then administered at 10 mg twice a day. However, oral dyskinesia abruptly occurred after he took the first dose of MPH-IR. The oral-buccal dyskinesia manifested with chewing movements of the jaw and repetitive tongue thrusting. The episode lasted for approximately four hours and resolved spontaneously. He stopped the medication the next day and there was no recurrence of dyskinesia symptoms.

Discussion

The two case reports herein summarise the courses of orofacial dyskinesia following the administration of MPH-IR in two Taiwanese school-age boys. These two patients took MPH-IR alone in the usual doses, and they did not take any other concomitant medications that might put them at risk of involuntary movement disorder. The orofacial dyskinesia subsided spontaneously after MPH-IR was discontinued. It is reasonable to conclude that the cases of dyskinesia were associated with MPH-IR administration.

MPH-IR is a short-acting stimulant agent with a duration of 4 hours; it reaches a maximum drug concentration two hours after oral administration. MPH potentially induces involuntary movement disorders, including tics, chorea and dyskinesia.[7] MPH-induced dyskinesia has been described as presenting in two different forms: late-onset and early-onset, based on the duration between MPH administration and the onset of dyskinesia.[5,6] Late-onset dyskinetic movements usually appear several weeks after the first use of MPH; patient A in our report showed a similar course of late-onset dyskinesia. By contrast, early-onset dyskinesia often occurs rapidly after drug intake and disappears soon after the discontinuation of the drug;[6] the course of patient B in our report resembles that of early-onset dyskinesia. Different hypotheses have been proposed for these two categories of dyskinesia. MPH as an indirect dopamine agonist, increasing the dopamine level in the striatum by blockade of dopamine transporters, might alter the sensitivity of dopamine receptors.[5] Late-onset dyskinesia is likely to be the result of hypersensitivity of dopamine receptors caused by chronic use of MPH. In early-onset dyskinesia, the involuntary movement in an "on-off" fashion might be related to an excessively high serum level of MPH.[3]

To the best of our knowledge, these are the first case reports showing that MPH-associated orofacial dyskinesia could occur in an Asian population. Previous reports on MPH-associated dyskinesia all focused on Caucasian populations.[2-6] Several pharmacogenetics studies reported that the human carboxylesterase 1 (*CES1*) gene variants can lead to clinically significant alterations in pharmacokinetics and the MPH response of carboxylesterase 1 substrates.[8-10] These studies found that *CES1* genetic variants are associated with MPH dose requirement for ADHD symptom reduction[9] and with occurrence of side effects.[10] There are significant discrepancies in the allelic frequency of *CES1* variants between different ethnicities.[8] Therefore, further studies are needed to clarify whether MPH-related movement disorder is less prevalent in Asian populations. Moreover, investigation of whether ethnic differences exist in the

pharmacokinetic, pharmacodynamic, and pharmacogenetic properties and adverse effects of MPH is warranted.

Our cases suggest that the potential for MPH-induced orofacial dyskinesia is also present in Asian populations. In addition to the common adverse effects of MPH, clinicians worldwide should pay attention to the risk of orofacial dyskinesia related to MPH at any time during treatment, even when patients are receiving standard doses of this agent.

Declaration of Interest

None

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