



CASE REPORT

Hiccups in Attention-Deficit/ Hyperactivity Disorder Under Methylphenidate Treatment

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ABSTRACT

Attention-deficit/ hyperactivity disorder is one of the most commonly observed pediatric psychiatric disorders in today's child and adolescent psychiatry clinics. Methylphenidate (MPH), a psychostimulant that acts on the dopaminergic system, is frequently used in treatment. Several studies have been performed concerning hiccups, and although some neurological mechanisms have been described, the pathophysiology is still unclear. However, neurotransmitter changes and hypo-/ hyperdopaminergic states are known to lead to hiccups. A 7-year-old boy was brought by his parents to our clinic due to hyperactivity, inability to remain still, frequent boredom, and compulsive talking. ADHD was diagnosed on the basis of DSM-5 diagnostic criteria following psychiatric assessments, and MPH was initiated. Hiccups had developed and persisting 3-4 hours after medication administration. Hiccups had resumed when the drug was administered again, and stopped after 3-4 hours. Resolution in cases of hiccups treated with MPH is probably associated with improvement of a hypodopaminergic state through MPH raising dopamine levels. Additionally, we think that MPH can also trigger hiccups (as in our case) by causing a hyperdopaminergic state. We therefore think that further studies are needed in order to clarify the etiology of hiccups and the relationship with drug interactions.

Keywords: Attention-deficit/ hyperactivity disorder, hiccup, methylphenidate, child

INTRODUCTION

Attention-deficit/ hyperactivity disorder (ADHD) is a chronic condition with adverse impacts on school/work life involving symptoms of inattention and hyperactivity-impulsivity. Immediate-release (IR) methylphenidate (MPH) (Ritalin) is the first MPH-based pharmacotherapy approved by the Food and Drug Administration (FDA) for the treatment of ADHD (1). Hiccups are sudden and involuntary contractions of the diaphragm and intercostal muscles. The condition is generally benign and self-limiting, but may be chronic under some circumstances

(2). Although the neurological components involved have been identified, the function of hiccups is uncertain. The neurotransmitters reported to be involved in the development of hiccups are dopamine, serotonin, and gamma-aminobutyric acid (GABA). Hiccups refractory to therapeutic measures has deleterious effects on patients' quality of life (3). Here, we report a case of hiccups developing following treatment in a boy started on MPH therapy with a diagnosis of ADHD. Written consent was received from the patient and his family for the publication of this report.

CASE PRESENTATION

A 7-year-old boy was the second of three children and was in the second year of school. He lived with his parents and two siblings. He was brought by his parents to our clinic due to hyperactivity and failure to do homework. His parents were frequently told by teachers of his

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inability to sit still, hyperactivity, failure to do homework and compulsive talking and that he was easily bored, and sometimes fought with his friends. His mother reported that he also displayed these symptoms at home. She also stated that these symptoms had been present for three years, which the family had not regarded it as necessary to seek medical attention since they regarded them as temporary, but that they had decided to present to our clinic when the complaints from his school intensified. The patient had no history of any systemic diseases and other psychiatric disorders. His developmental history revealed that the pregnancy was normal, he was born on term weighing 3500 g, no complications occurred during delivery, but the mother smoked during pregnancy. In the family history, the father was also reported to be hyperactive, untidy, and impatient. The patient's examination findings were as follows: a male patient 120 cm in height and weighing 26 kg. In the psychiatric evaluation; he established eye contact, talked compulsively, and was impatient, and hyperactive. He was alert and oriented time, place, person, and situation. His speech was fluent and goal-directed. He had no experiences of hallucinations. He had no thoughts of delusions, paranoia, homicidal or suicidal ideations. He appeared to show no depressed or elevated mood. The Turkish versions of the Turgay DSM-IV-Based Screening Scale for DSM-IV Disruptive Behavior Disorders were used to evaluate the severity of his symptoms (attention deficit score was 23, hyperactivity/ impulsivity score was 25 (4). The clinical global impression-severity of illness (CGI-SI) score was 6 (severely ill). ADHD was diagnosed on the basis of DSM-5 diagnostic criteria following psychiatric assessments, and Methylphenidate-Immediate Release (MPH-IR) was initiated. Two days later, the patient was brought back to our clinic by his mother. The mother stated that on the previous day she had given the patient his medication after breakfast and sent him to school, but that the school had called 1-2 hours subsequently, and his teacher informed her that hiccups had developed, and that this condition was persisting. The hiccups stopped 1-2 hours after the mother picked up the patient from school, and she did not give him the medication again.

We told the mother to administer the medication when they returned home, but that the drug could be modified if hiccups recurred. The child was brought back the next day, and we were informed that hiccups had resumed when the drug was administered, and stopped after 3-4 hours. The hiccups persisting 3-4 hours after medication administration, and this being repeated suggested that the MPH might have been the cause. His Naranjo adverse drug reaction probability scale score was 6 for the drug (5). It suggests a probable association between MPH and hiccups. MPH was therefore stopped, and atomoxetine therapy was started. We are managing ADHD symptoms with atomoxetine therapy (36 mg/day) for the last three months with no signs of hiccups.

DISCUSSION

We report a male patient with ADHD developing hiccups following MPH use. The hiccups resolved entirely following discontinuation of MPH.

Somatic and sensory signals transmitted by afferent fibers consisting of the phrenic, vagus, and sympathetic nerves are carried to the diaphragm and intercostal muscles by means of efferent fibers. The contractions that occur in the diaphragm and intercostal muscles due to this stimulus are known to cause hiccups (6). However, less is known about the central processes involved in hiccups, an involuntary medullary reflex, and the mechanism involved is thought to be regulated by a neuronal network in the lower brain stem (7). The neurotransmitters thought to be involved in the development of hiccups are dopamine, serotonin, and GABA. Changes in serotonin and GABA and hypo-/hyperdopaminergic states are known to play a significant role in hiccups development, and drugs that affect these neurotransmitters are effective in the treatment of the condition (8).

Although the effect mechanism is not fully understood, MPH principally affects catecholaminergic activity in the prefrontal cortex and striatum. It produces this effect by increasing dopamine transmission through more than one mechanism. MPH produces more than one effect by blocking the dopamine transporter, preventing inhibition

of dopamine D2-autoreceptors, causing activation of D1 receptors in the postsynaptic neurons, and increasing the level and effect of extracellular dopamine. In addition, MPH mediates the stimulation of the α -2 noradrenergic receptor and the dopamine D1 receptor in the cortex (8). The efficacy, safety and side-effect profile of MPH are well known. The most common side-effects are difficulty in falling asleep, decreased appetite, abdominal pain and headache. However, although there have been studies reporting that MPH is effective in the treatment of hiccups (9), no side-effect of causing hiccups has previously been described.

Hypo-/hyperdopaminergic states are reported to play a role in the development of hiccups. Antipsychotics may be thought to cause hiccups in some patients (3,10) and to lead to hiccups during the treatment of some cases by causing relative hypodopaminergic and also hyperdopaminergic states (10). Interestingly a case had hiccups arising in an adolescent patient after adding aripiprazole treatment to extended-release methylphenidate (11). This shows that the balance of the dopaminergic system is involved in the pathophysiology. An increase or decrease in the dopaminergic system

being capable of triggering or treating hiccups may also apply to MPH. Resolution in cases of hiccups treated with MPH is probably associated with improvement of a hypodopaminergic state through MPH raising dopamine levels. Additionally, we think that MPH can also trigger hiccups (as in our case) by causing a hyperdopaminergic state. The complex pathogenesis of hiccups and the fact that this has not yet been completely explained, together with MPH and other psychotropic drugs both triggering and curing hiccups, shows that there is still much remaining to be understood. We therefore think that further reports/ studies are needed in order to clarify the etiology of hiccups and the relationship with drug interactions.

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REFERENCES

- Childress A, Mehrotra S, Gobburu J, McLean A, DeSousa NJ, Incledon B. Single-dose pharmacokinetics of hld200, a delayed-release and extended-release methylphenidate formulation, in healthy adults and in adolescents and children with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* 2018;28(1):10-8. [\[CrossRef\]](#)
- Nausheen F, Mohsin H, Lakhan SE. Neurotransmitters in hiccups. *Springerplus* 2016;5(1): 1357. [\[CrossRef\]](#)
- Ray P, Zia UI Haq M, Nizamie SH. Aripiprazole-induced hiccups: a case report. *Gen Hosp Psychiatry* 2009;31(4):382-4. [\[CrossRef\]](#)
- Ercan ES, Amado S, Somer O, Cikoglu S. Development of a test battery for the assessment of attention deficit hyperactivity disorder. *Turkish Journal of Child and Adolescent Mental Health* 2001;8(3):132-45.
- Kose S, Akin E, Cetin M. Adverse drug reactions and causality: the Turkish version of Naranjo Adverse Drug Reactions Probability Scale. *Psychiatry and Clinical Psychopharmacology* 2017;27(2):205-6. [\[CrossRef\]](#)
- Becker DE. Nausea, vomiting, and hiccups: a review of mechanisms and treatment. *Anesth Prog* 2010;57(4):150-6. [\[CrossRef\]](#)
- Arita H, Oshima T, Kita I, Sakamoto M. Generation of hiccup by electrical stimulation in medulla of cats. *Neurosci Lett* 1994;175(1-2):67-70. [\[CrossRef\]](#)
- Wilens TE. Effects of methylphenidate on the catecholaminergic system in attention-deficit/hyperactivity disorder. *J Clin Psychopharmacol* 2008;28(3Suppl.2):S46-53. [\[CrossRef\]](#)
- Kranke P, Eberhart LH, Morin AM, Cracknell J, Greim CA, Roewer N. Treatment of hiccup during general anaesthesia or sedation: a qualitative systematic review. *Eur J Anaesthesiol* 2003;20(3):239-44. [\[CrossRef\]](#)
- Kutuk MO, Tufan AE, Guler G, Yildirim V, Toros F. Persistent hiccups due to aripiprazole in an adolescent with obsessive compulsive disorder responding to dose reduction and rechallenge. *Oxf Med Case Reports* 2016;4:66-7. [\[CrossRef\]](#)
- Kutuk MO, Guler G, Tufan AE, Kutuk O. Hiccup due to aripiprazole plus methylphenidate treatment in an adolescent with attention deficit and hyperactivity disorder and conduct disorder: a case report. *Clin Psychopharmacol Neurosci* 2017;15(4):410-2. [\[CrossRef\]](#)