



LETTER TO THE EDITOR

Methylphenidate and indomethacin induced visual hallucination: a case report

Kemal Utku Yazici¹, Ipek Percinel Yazici¹

¹Firat University, Faculty of Medicine, Department of Child and Adolescent Psychiatry, Elazig - Turkey

Dear Editor,

Attention deficit hyperactivity disorder (ADHD) is one of the most common neuropsychiatric disorders seen in childhood and adolescence. Psychopharmacologic agents are known to be the most effective treatment options for ADHD. The most frequently researched and prescribed drug group in this regard is psychostimulants (1). Methylphenidate is the most commonly used stimulant for the treatment of ADHD (2). Indomethacin, a nonsteroidal anti-inflammatory drug (NSAID), is a non-selective inhibitor of cyclooxygenase 1 and cyclooxygenase 2 enzymes, which play a role in prostaglandin synthesis from arachidonic acid (3). Indomethacin is quite often used as an anti-inflammatory and analgesic drug.

A 14-year-old girl was admitted to our clinic with complaints of attention deficit, lack of concentration in school lessons, forgetfulness, procrastination, lack of being organized, excessive talking, and impulsivity. As a result of our assessments, the patient was diagnosed with ADHD, and 27 mg/day of long-acting methylphenidate treatment was initiated. The case was followed regularly in our polyclinic. The methylphenidate dose was increased to 36 mg/day after one month in view of moderate benefit of the treatment and absence of any side effects. No drug-related problems were identified in controls performed within two months after the dose increase. Then, the patient presented outside the scheduled follow-up appointments with the complaint of “seeing strange things.” She reported that

while sitting at home, she had seen very short strange creatures resembling dwarves with non-human faces. Those creatures looked hostile to her and laughed at her after talking among themselves. The complaints had begun about 48 hours prior to her admission to the hospital. From that time, she could not stay at home alone. The patient had been using long-acting methylphenidate for a total of three months when she presented to us with psychotic symptoms. She did not have any psychiatric or organic disease in her medical history and her family history. According to the information obtained from her family, she had experienced menarche four days ago and she was using indomethacin in the last three days due to intense dysmenorrhea. The patient’s mother stated that she had also given her daughter indomethacin several times for complaints such as headache or abdominal pain before she started treatment with methylphenidate. However, no complications were observed at those times when the drug was given. There was no other report of disease, trauma, or drug use. There was no disorder that could cause psychotic findings in the organic examinations of the patient. Her current psychotic complaints, which had been treated regularly with methylphenidate therapy for about three months without showing any side effects associated with methylphenidate, were thought to be related to the subsequent use of indomethacin. The patient, having benefited from methylphenidate treatment, was recommended to stop using indomethacin. The methylphenidate treatment was continued as before. After cessation of indomethacin,

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Correspondence: Kemal Utku Yazici, Firat University, Faculty of Medicine, Department of Child and Adolescent Psychiatry, Elazig - Turkey

Phone: +90 424 233 35 55 **E-mail:** dr.kemal.utku@outlook.com

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the patient's visual hallucinations quickly disappeared (within 48 hours). The psychotic symptoms did not recur in the clinical follow-up period.

Methylphenidate has been used for many years in an effective and reliable way in the treatment of ADHD during childhood and adolescence. In general, methylphenidate is quite well tolerated. Side effects most commonly reported with methylphenidate treatment are loss of appetite, insomnia, and irritability. The side effects are mostly mild and temporary (4).

Besides mild and temporary side effects, there are also studies in the literature that have reported psychotic findings related to the use of methylphenidate. Visual, auditory, and tactile hallucinations during treatment with methylphenidate at therapeutic doses have been found (5-9). Psychotic symptoms thought to be associated with methylphenidate have been seen rarely, usually with acute onset, and disappeared in a short period of time after cessation of medication (8). In a meta-analysis reviewing 49 randomized controlled trials, psychotic/manic symptoms were observed in 11 out of 743 cases using drugs for ADHD treatment (the rate per 100 person-years in the pooled active drug group was 1.48). There were no psychotic/manic symptoms in 420 ADHD patients receiving the placebo treatment. The most common psychotic/manic symptoms were observed in the treatment of transdermal methylphenidate and dexamphetamine, respectively (10). In another study reviewing medical records from the period between 2001 and 2014, psychotic symptoms were observed in only 103 out of 20,322 patients between ages of 6 and 19 years that had received methylphenidate therapy during this time (11). It is not exactly known how methylphenidate caused the psychotic symptoms. The basic effect mechanism of methylphenidate is to increase dopamine levels in the synaptic gap (12). It has been indicated that this increase may be a risk factor for psychotic symptoms, and that methylphenidate may cause psychotic symptoms this way (13).

Indomethacin, an NSAID agent, is often used as an analgesic treatment option. There are studies in the literature reporting psychotic symptoms induced by NSAIDs (14). There have also been publications indicating psychotic symptoms during indomethacin use (15-17). Although the underlying mechanisms of psychotic symptoms due to indomethacin have not been fully understood, indomethacin has been documented to inhibit prostaglandin synthesis and thus increase dopamine levels indirectly, which may cause psychotic symptoms (18).

Although it has been suggested in the literature that psychotic symptoms associated with methylphenidate usually begin shortly after starting the drug, some studies have noted that psychotic symptoms can also be observed after months or years of methylphenidate use (5,8). No psychotic findings were observed when our patient used only methylphenidate. Visual hallucinations emerged during the period when indomethacin was being used to treat dysmenorrhea (she had been using methylphenidate for about three months). In addition, it was learned from her family that the patient sometimes had used indomethacin for a short time (max. 1 week) also before using methylphenidate and experienced no problem. Moreover, psychotic symptoms quickly disappeared only after cessation of indomethacin therapy. The psychotic side effects observed in our case may be associated only with the use of indomethacin. However, the current situation makes us think that simultaneous use of both drugs may strengthen their mutual influence on psychotic side effects; although they did not cause such a problem when used individually. This possibility is crucial in terms of clinical practice.

Methylphenidate increases the level of dopamine in the synaptic gap (12). Indomethacin has also been reported to increase dopamine levels indirectly by inhibiting prostaglandin synthesis (18). These two drugs might potentially affect each other, increase the dopamine level further, and thus cause psychotic symptoms. In our case, no psychotic side effect was observed in the period when methylphenidate and indomethacin were used separately, but visual hallucinations appeared when they were used together. As far as we know, this was the first reported case that has demonstrated psychotic symptoms due to concurrent use of both agents.

In conclusion, in rare cases, drug-drug interactions can lead to dangerous situations for patients. It is vital for clinicians to pay attention to this possibility in the presence of severe psychiatric symptoms that occur during unexpected situations. In this regard, our study is considered to be important. However, there is a need for further detailed studies in order to clarify this issue.

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