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CASE REPORT

Olanzapine-induced atypical neuroleptic malignant syndrome in an adolescent man with anorexia nervosa

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Introduction

Anorexia nervosa (AN) is a serious mental illness that causes significant physical, emotional, cognitive, and social impairments. AN most often develops during adolescence or young adulthood and has high mortality and morbidity rates, in addition to cost burden. Current treatment of AN is multidisciplinary and is typically with a combination of medical, nutritional, and psychological interventions [1] . Antipsychotic medications have been especially used for weight gain and to treat body focused delusional thoughts in adolescent patients with AN [2]. Olanzapine is the most prominent second-generation antipsychotics (SGA) used for the treatment of this condition. However, although it is reported that these drugs are safe to use in adolescents with AN, side effects such as neuroleptic malignant syndrome (NMS) may vary in both the presenting and progressing features in patients with AN.

NMS is a rare, idiosyncratic, and potentially fatal complication of antipsychotic medication. Cardinal features of NMS are muscle rigidity, hyperthermia, autonomic instability, and altered mental state. Laboratory findings are non-specific, but leukocytosis is common, and the levels of creatine kinase (CK) are often elevated. Approximately 66 % of NMS cases develop within the first week of initiating of antipsychotic treatment or a change of dose, and almost all cases develop within 30 days [1]. We report a case of an adolescent man with AN, who developed symptoms consistent with NMS after 2 days of treatment with a low dose of olanzapine, and although the symptoms of NMS had been resolved, these symptoms recurred after a month.

Case report

A 17-year-old man, a student in the first year of high school, was referred to our pediatric gastroenterology clinic with weight loss, restriction of energy intake during the day, and bingeing, followed by vomiting. When he was admitted to our clinic, he was sitting in the fetal position. At the time of admission, he was 164 cm tall and his weight was 32 kg, which equated to a BMI of 11.9 kg/m^2. His symptoms started at the age of 15, after he moved to another location. Separating from his old friends and neighbors caused him severe stress. His first pathological eating behavior was binge eating, followed by self-induced vomiting. Later, his vomiting became spontaneous. He was not performing caloric restriction or cardiovascular exercise. Because of vomiting, his weight was 32 kg over the ensuing 18 months. He had reached 42 kg (BMI 15.6) with nutritional rehabilitation and cognitive behavioral therapy within the next 4 months. After a discussion with his family, his vomiting started again during the fourth month of his treatment. To control the patient's vomiting and to increase his weight, he was prescribed olanzapine 5 mg/day. He had not received any pharmacological treatment before olanzapine. On his second day of taking olanzapine, he developed high fever (axillary temperature was 40 °C) and tachycardia (120 beats/min). His blood pressure was 95/65 mm Hg. Muscle rigidity was present in

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the four extremities within 12 h of the high fever. His mental status was stuporous, and there was no sign of meningeal irritation. Laboratory evaluation showed an initial serum CK level of 72 IU/L, and leukocyte count was 7800 mm^3. Brain computed tomography was normal. His high fever, which did not respond to antipyretics such as paracetamol and ibuprofen, dropped spontaneously after about 30 h. Along with the fever, the muscle rigidity reduced. Despite discontinuation of the olanzapine and the initial reduction in the high fever, the patient's temperature elevated to 40.5 °C after 24 h, and this fever continued for 12 h. The laboratory CK level was normal (176 IU/L). Because the patient's temperature elevated to 39 °C again 10 h later and because of fluctuations in his mental status, he was transferred to the intensive care unit. Although the serum CK level was elevated (535 IU/L), his leukocyte count was normal (6800 mm^3). Amantadine (200 mg/day) was added to his treatment regimen while he was in the intensive care unit. After his vital signs normalized, amantadine was discontinued after 4 days, and he was transferred to our clinic. During the following 4 weeks of treatment, he had reached 44 kg (BMI 16.4), and his vital signs were normal. Then, 30 days after his last high fever, his temperature elevated to 40 °C. Although his leukocyte levels were normal (7800 mm^3), his CK levels were very high (5651 IU/L). Within 5 days, the CK level decreased to 127 IU/L. His chest radiograph and urine analysis showed no signs of infection. He had no history of food and drug allergies. He was not found to have any medical condition for his fever. The patterns of the level of body temperature and CK are summarized in Fig. 1. Almost 37 days from the onset of NMS, his axillary temperature was 37 °C, his heart rate measured 67 beats per minute, and his blood pressure was 85/65 mm Hg.

Discussion

SGA are recommended to treat body misperception and for weight gain in adolescents with AN [2]. Although these drugs were thought to be safe, they can cause serious adverse effects including NMS. The classic form of NMS can be easily recognized, but its onset, presentation, progression, and outcome are often heterogeneous. Our patient had muscle rigidity, fever, and autonomic instability, and later developed increased level of CK. The symptoms of this case were consistent with the diagnosis of NMS according to DSM-5.

To the best of our knowledge, this is the first reported case of NMS in AN. NMS predominantly affects young men, and other predisposing factors include preexisting medical and neurological disorders, mental retardation, medication factors, iron deficiency, dehydration, and psychomotor agitation [1]. He did not have any of these predisposing factors. Although his metabolic parameters were under control, the fact that our patient was male and that he had AN, which has metabolic consequences, may have put him at an increased risk of NMS.

Approximately 16 % of NMS cases occur within the first 24 h of antipsychotic administration, 66 % occur within the first week, and when antipsychotic treatment is discontinued, NMS is self-limited in most cases [1]. The

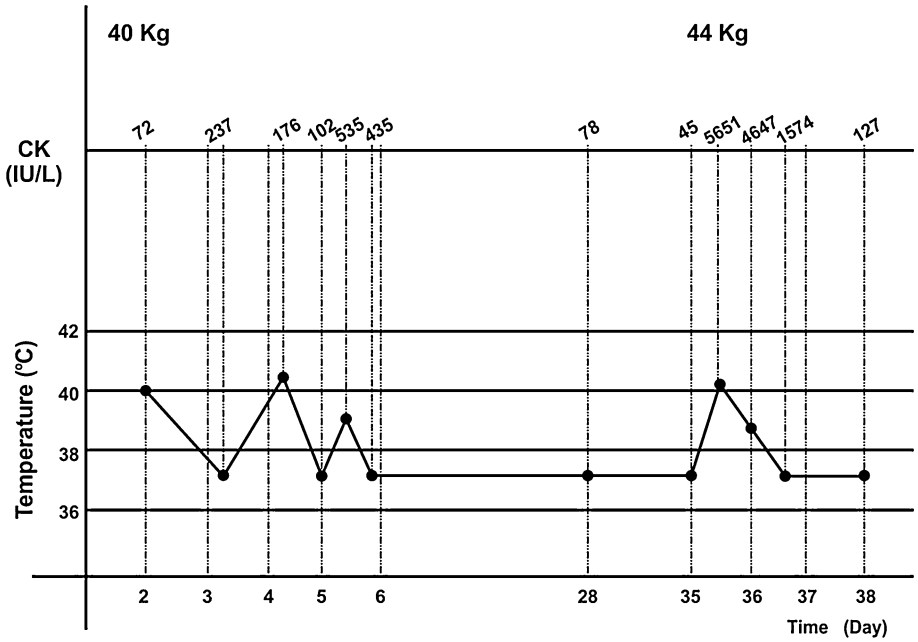

Fig. 1 Levels of body temperature and CK within the process

recovery time after drug discontinuation is within 30 days in nearly all cases [1]. The onset of symptoms in our case is compatible with the classical form of NMS. Although the drug was discontinued, NMS developed again after 30 days. In the literature, a case of "atypical intermittent NMS" with olanzapine has been described [3]. In that particular case, there was no muscle rigidity, CK elevation, or leucocytosis, but hyperthermia, altered mental status, and autonomic instability were present, and the patient's body temperature was fluctuating and included a 10-day normothermic period. Our patient also had a fluctuating body temperature and 30-day normothermic period. However, in our case, NMS developed 30 days after the discontinuation of olanzapine, and this differs from the other case that became normothermic and did not develop fever after olanzapine was stopped. It is possible that NMS had continued, but it had been controlled by amantadine, or it may have recurred inexplicably.

Another interesting feature of our case was that the CK levels did not increase when the NMS first presented, rather the levels increased 30 days later. During the next month, the patient gained 4 kg and increased his muscle mass. The increase in serum CK is considered a hallmark of muscle involvement, and CK is released in the serum in case of muscle damage. Depending on the increase in our patient's muscle mass, the CK levels may have elevated 30 days later.

Conclusion

AN is a serious mental illness, and psychopharmacological treatment plays an important role in the management of patients with AN. Olanzapine is one antipsychotic agent used for the treatment of this condition. Although olanzapine was thought to be safe, it can cause serious adverse effects including NMS. Here, we reported a case of an adolescent man with AN who developed symptoms consistent with NMS after 2 days of treatment with a low dose of olanzapine. NMS may vary in both the presenting and progressing features in patients with AN. Although the administration of the drug was discontinued, NMS may develop up to a month later. Clinicians should bear in mind that the condition is heterogeneous. On the other hand, this case showed that we need to be careful while prescribing antipsychotic medications to pediatric cases and for patients with AN who are severely underweight. In addition to this, further studies are needed to investigate the different manifestations of NMS.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki and International Conference on Harmonisation/Good Clinical Practice guidelines and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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