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Antipsychotic-induced hyperthermia in patients with behavioral and psychological symptoms of dementia

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Antipsychotic drugs have been used off-label in clinical practice for treatment of behavioral and psychological symptoms of dementia (BPSD). However, vascular accidents and pneumonia may be associated with the use of antipsychotics in dementia patients [1]. Elderly patients with dementia who are being treated with antipsychotic drugs may suddenly develop hyperthermia. In many cases, hyperthermia is caused by infectious diseases such as aspiration pneumonia or pyelonephritis, but some cases of hyperthermia are unexpectedly seen in psychiatric practice even in the absence of any obvious infectious disease. We present a case of antipsychotic-induced hyperthermia with BPSD.

A 77-year-old man who had suffered Alzheimer's disease for the past several years was admitted to our hospital because of wandering, agitation, and violent behavior associated with progression of dementia. He was 160 cm tall, weighed 62 kg (BMI: 24.2), and was not malnourished. Physical examination revealed no abnormalities. He had received no medications for 6 months since donepezil had been discontinued because of ineffectiveness. Treatment with olanzapine 5 mg/day was initiated, and the agitation was slightly relieved, but the wandering persisted. On the sixth day after the start of olanzapine treatment, the patient suddenly developed hyperthermia, with a fever of 39.7ºC. There were no findings except general malaise due to hyperthermia. The next day's blood examination revealed a white blood cell count of 5,600/mm3 and a CRP value of 0.4 mg/dL, findings that were not indicative of inflammation. Other routine blood examination values were also within the range of normal. However, because the patient's AST/ALT ratio was more than 2, we decided to examine his creatinine kinase (CK) level [2], and found that the CK value had increased to 1,890 IU/L. Treatment with olanzapine was discontinued, and a fluid infusion was started. On the third day after the discontinuation of olanzapine, the patient's fever had declined to 37.6ºC, and on the fourth day after discontinuation, his temperature had returned to a normal level of 36.4ºC, with a normal CK value of 88 IU/L. At this time, the patient's AST and ALT values were 19 IU/L and 14 IU/L, respectively. The patient's AST/ALT ratio was therefore less than 2 when his temperature had returned to normal. The clinical course of this patient is shown in Figure 1.

The present case is hyperthermia of unknown origin without infectious findings. Although the patient exhibited no symptoms such as muscle rigidity or excess perspiration that would be suggestive of neuroleptic malignant syndrome, fluid infusion after discontinuation of antipsychotic therapy relieved the patient's fever. Therefore, this could be a case of an antipsychotic-induced hypodopaminergic state leading to hyperthermia. The alteration in dopamine transmission induced by the central blockade of dopamine D1 and D2 receptors impairs running performance by decreasing tolerance to heat storage in experiments using rats [3]. This blockade of D1 and D2 receptors also blocks the dissipation of exercise-induced heat and metabolic rate recovery during the post-exercise period [3]. Animal experiments have confirmed that blockade of central D1 and D2 receptors impairs thermoregulation and metabolic rate

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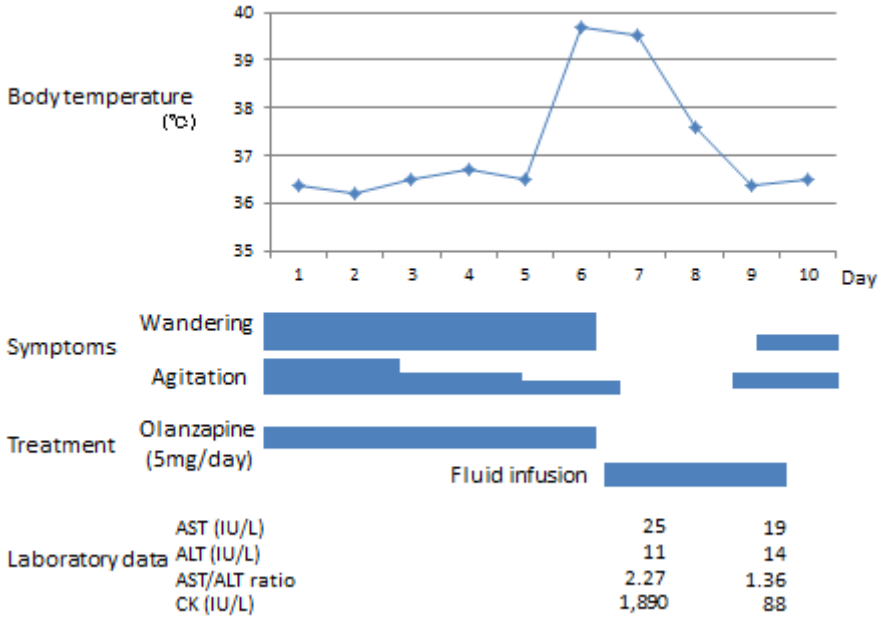
regulation, leading to hyperthermia during and after exercise [4]. Central D1 and D2 receptors are thought to be essential for heat balance and exercise performance [5]. If dementia patients with central D1 and D2 receptors blocked by antipsychotics wander for a long time, they are likely to develop hyperthermia due to impaired thermoregulation during and after wandering. Increased CK levels may be caused by impaired central metabolic rate regulation resulting from blockade of dopamine receptors. In addition to the effects of an antipsychotic-induced hypodopaminergic state, psycho-physiological vulnerabilities such as mild dehydration due to psychomotor agitation and predisposing environmental conditions such as air-conditoning may play an important role in thermoregulation. Recently, the incidence of definite and fatal neuroleptic malignant syndrome (NMS) has decreased dramatically, probably because second-generation antipsychotics put patients at lower risk of developing NMS due to their less potent dopamine receptor blockade. However, a kind of non-fatal NMS-like condition that does not strictly meet the criteria for NMS is occasionally observed in routine psychiatric practice, so it remains unclear whether this type of antipsychotic-induced hyperthermia without muscle rigidity represents early or impending NMS [6].

If hyperthermia occurs in elderly patients with BPSD treated with antipsychotic drugs, exercise-induced heat must be suspected. A routine blood examination result that may suggest this condition is an AST/ALT ratio of about 2, despite both AST and ALT being within the range of normal; this suggests that CK levels are elevated [2]. However, because a hypodopaminergic state is likely to cause concomitant aspiration pneumonia [7], the possibility of antipsychoticinduced exercise-intolerance fever should not be ruled out even in dementia patients with high fever and infectious findings.

Figure 1. Clinical Course of Patient With Antipsychotic-Induced Exercise-Intolerance Fever



REFERENCES

[1] Maher AR, Maglione M, Bagley S, Suttorp M, Hu JH, Ewing B, Wang Z, Timmer M, Sultzer D, Shekelle PG. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. JAMA 2011;306:1359-1369.

[2] Nagamine T.: How to predict CK values using AST/ALT ratio. In "To Predict and Prevent Antipsychotic-associated Adverse Events – Beyond dopamine antagonism" Igakushoin, Tokyo, 2009, pp. 116-119. (in Japanese)

[3] Balthazar CH, Leite LH, Ribeiro RM, Soares DD, Coimbra CC. Effects of blockade of central dopamine D1 and D2 receptors on thermoregulation, metabolic rate and running performance. Pharmacol Rep 2010;62:54-61.

[4] Chaperon F, Tricklebank MD, Unger L, Neijt HC. Evidence for regulation of body temperature in rats by dopamine D2 receptor and

possible influence of D1 but not D3 and D4 receptors. Neuropharmacology 2003;44:1047-1053.

[5] Brown PL, Bae D, Kiyatkin EA. Relationships between locomotor activation and alterations in brain temperature during selective blockade and stimulation of dopamine transmission. Neuroscience 2007;145:335-343.

[6] Picard LS, Lindsay S, Strawn JR, Kaneria RM, Patel NC, Keck PE Jr. Atypical neuroleptic malignant syndrome: diagnostic controversies and considerations. Pharmacotherapy 2008;28:530-535.

[7] Nagamine T. Serum substance P levels in patients with chronic schizophrenia treated with typical or atypical antipsychotics. Neuropsychiatr Dis Treat 2008;4:289-294.