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Letter to the Editor / Editöre Mektup

Clozapine – Induced Neuroleptic Malignant Syndrome Associated with Rapid Dose Escalation

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Dear Editor,

Neuroleptic malignant syndrome (NMS) is a rare, dangerous, and life-threatening adverse reaction to antipsychotic drugs (1). NMS is strongly associated with first-generation antipsychotics (1), but it also occurs with second generation antipsychotics (2). The blockage of dopaminergic transmission of D2 receptors causes NMS symptoms (3). Clozapine-associated NMS is rarely seen and differs from those with other atypical antipsychotics because it is less likely to show extrapyramidal symptoms (2). We would like to report a rare case of incomplete NMS after a rapid dose escalation of clozapine.

A 50-year-old man who had no history of NMS was diagnosed with schizophrenia 32 years ago and has been treated with 400–600mg of clozapine every day for 14 years because he failed to adequately respond to other neuroleptics. Because of epileptic seizures, valproate (500mg/day) was added over time. His clinical condition was good with the treatment of clozapine at 450mg/day during the last year. At one of his follow-up visits, clozapine dose was increased to 550mg/day because psychotic symptoms such as visual hallucinations worsened by stressful events related to his mother's illness. Two days later, the patient developed confusion. Upon admission to the emergency department, his body temperature was 38.9°C, and the creatine kinase (CK) level was elevated up to 426U/L; (normal range, 49–397U/L) physical examination revealed rigidity and computerized tomography (CT) was normal. This condition was diagnosed as NMS and he was admitted to the neurology intensive care unit. All pharmacotherapy was discontinued and supportive treatment was initiated. After 4 days, his clinical status and repeated laboratory tests returned to normal. Ten days after cessation of clozapine, psychotic symptoms re-emerged, and amisulpride (800mg/day) was started. Because there was no improvement in his clinical status, he was switched to clozapine, and the dose was very gradually increased to 200mg/day under the

control of vital signs and laboratory tests. The psychotic symptoms resolved and the patient stayed in good health at this dose without any recurrence of psychiatric symptoms and NMS.

In this case, clozapine was readministered because of his history of unresponsiveness to other antipsychotics. The slow titration and low dose of clozapine were intended to minimize the risk factors of NMS, such as a high dose and rapid dose escalation. Serotonin syndrome, malignant hyperthermia, malignant catatonia and central anticholinergic syndrome can resemble NMS as they share common features of hyperpyrexia and dysautonomia. Hyperreflexia and gastrointestinal symptoms are typical features of serotonin syndrome. Malignant hyperthermia is most commonly seen due to anesthetic agents. Malignant catatonia was excluded as the physical examination did not reveal any remarkable catatonic symptoms. Rigidity and elevated CK levels are not common in central anticholinergic syndrome. Our case is consistent with the literature showing that clozapine-associated NMS cases had fewer extrapyramidal side effects and slightly elevated CK levels (4). However, there are reports of "typical" NMS in association with clozapine (5). Our report describes an atypical form of clozapine-associated NMS and points to the importance of early diagnosis and treatment of this adverse effect.

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