Neuroleptic Malignant Syndrome During Long-Term Antipsychotic Combination Treatment: a Case Report

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ÖZET

Uzun süreli kombine antipsikotik tedavi sırasında nöroleptik malign sendrom: Olgu sunumu

Nöroleptik Malign Sendrom (NMS) genellikle antipsikotik kullanımı ile görülen, nadir karşılaşılan, ancak yaşamı tehdit edebilen idiosinkratik istenmeyen bir etkidir. Yüksek ateş, otonomik dengesizlik, ekstrapiramidal bulgular ve bilinç değişiklikleri ile karakterizedir. Laboratuvar tetkiklerinde yüksek kreatin kinaz düzeyi, karaciğer ve böbrek işlevlerinde bozulma, lökositoz ve elektrolit dengesizliği görülebilir. Çeşitli demografik, hasta ve tedaviye ait özellikler ve çevresel faktörler NMS riskini artırır. Bu olgu bildiriminde, mental retardasyon, parenteral, yüksek doz ve uzun süreli tipik antipsikotiklerin birlikte kullanımı gibi bir kaç risk etkeni olan hastada NMS'un klinik özellikleri ve başetme tartışılmıştır.

Anahtar kelimeler: Nöroleptik malign sendrom, antipsikotikler, mental retardasyon

ABSTRACT

Neuroleptic malignant syndrome during long-term antipsychotic combination treatment: a case report

Neuroleptic malignant sydnrome (NMS) is a rare but potentially life-threatening idiosyncratic adverse reaction, usually seen with antipsychotic treatment. It is characterized by fever, autonomic instability, extrapyramidal syndrome and altered mental state. Raised serum creatine kinase level, impaired liver and kidney function tests, leucocytosis and electrolyte disturbance may be the accompanying laboratory features. Various demographic, patient-medication and environmental factors increase the risk of NMS. In this case report, the clinical characteristics and management of NMS in a patient who has several risk factors such as mental retardation, use of parenteral, high dose typical antipsychotic combination for long duration is discussed.

Key words: Neuroleptic malignant sydnrome, antipsychotics, mental retardation

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INTRODUCTION

Neuroleptic Malignant Syndrome (NMS) is a rarely encountered but unpredictable and potentially mortal syndrome related to antipsychotic use. Typical symptoms include fever, muscular rigidity in the form of gear-wheel and lead-pipe phenomenon, changes in mental functions (confusion, agitation, aggression, or catatonia), disorders of the autonomous nervous system (hypertension, tachycardia, tachypnea, sweating, urine incontinence), and a change in several blood values (decrease in serum electrolytes, increase in creatinephosphokinase [CPK], leucocytosis). Muscular rigidity is frequently associated with muscular necrosis, mioglobinuria, and high serum CPK level (1,2).

NMS is generally encountered when starting or rapidly increasing doses of high-potency antipsychotic drugs and is considered to be connected to dopamine receptor blockade. NMS is reported to develop with all atypical antipsychotics, and even with other drugs including antidepressants.

The prevalence of NMS is between 0.07 percent and 2.2 percent. Mortality in NMS may vary widely from ten to 70 percent depending on the intensity of symptoms and timing of the treatment approach (3).

The treatment approach consists of immediately discontinuing use of the causative agent(s), correcting body fluid-electrolyte levels through supportive treatment (care, cooling, rehydration), and administering anticoagulant drugs as well as benzodiazepine, clonazepam, bromocriptine, and other dopamine agonists, and starting dantrolene treatment (4,5).

In this case report, a patient with psychosis due to mental retardation who presented with NMS is discussed

Table 1: Laboratory findings in the process of discontinuing antipsychotic treatment and fluid replacement

	Day 1	Day 2	Day 3	Day 6	Day 11	Day 16	Day 17	Day 22
Leucocyte (4,1-11,2x103/µL)	13,0	8,2	9,3	-	-	7,9	6,5	6,3
UREA (10-45 mg/dL)	68	90	146	131	74	25	35	26
CREATININE (0,3-1,3 mg/dL)	2,9	3,9	6,5	6,9	2,9	1,4	1,4	1,2
AST (5-45 IU/L)	931	978	809	154	52	40	40	26
ALT (5-40 IU/L)	220	286	380	17	4	6	9	10
CPK (20-200 IU/L)	36.697	44.118	25.121	3.814	572	397	347	178
Na (135-145 mmol/L)	137	138	137	136	148	144	140	139
K (3,5-5,1 mmol/L)	3,9	3,9	5,3	3,5	4,2	3,8	3,6	3,8

in light of the literature. The patient had been receiving long-term, typical high-dose combined antipsychotic treatment in oral and depot form but developed NMS following the addition of another typical intramuscular (IM) antipsychotic due to an increase in his symptoms. He suffered severe liver and kidney failure, but recovered through intense and supportive benzodiazepine and bromocriptine treatment.

CASE

A 54-year-old single female patient was admitted to our hospital's chronic diseases department with the diagnosis of "moderate level mental retardation and not otherwise specified (NOS) psychotic disorder" according to DSM-IV-TR diagnosis and was receiving psychiatric care and treatment. The patient's long-term psychiatric treatment was haloperidol 30 mg/day, biperidene 4 mg/day, chlorpromazine 300-400 mg/day, and fluphenazine decanoate 25 mg depot IM once a month. Upon the development of excitation syndrome as a result of an exacerbation of psychotic symptoms (persecution and reference delusions, hallucinative behavior), zuclopenthixol amp 50 mg and clonazepam 1 mg/day were added to the patient's treatment. On the third day following the excitation, the fluphenazine decanoate in her routine treatment was administered as 25 mg depot IM. About one week after the onset of excitation, the patient stopped eating and her clinical state became even more severe and mental dimness, drowsiness, ataxia, rigidity in the lower and upper extremities were also observed. On the tenth day, leucocyte (WBC: 13.0x103/µL), hypotension (80/50 mmHg), fever (37.5 °C), elevated CPK (36,697 IU/L) and a rise in liver enzymes were detected.

The patient was admitted to intensive care with a pre-diagnosis of "NMS" as a result of the neurology consultation made on the same day. Her antipsychotic treatment was stopped and intravenous (IV) fluid replacement was started. Because there was a reduction in rigidity the next day, the neurology clinic moved away from the diagnosis of NMS, but the patient, who was transferred to the internal diseases department, continued to receive follow-up care the diagnosis of NMS. On the second day of fluid replacement, it was detected that elevated CPK (44.118 IU/L), 37.5 °C fever, rigidity, and a rise in KC enzymes persisted, and bromocriptine 5 mg/day was added to the treatment. Laboratory findings in the process of stopping antipsychotic treatment and fluid replacement are shown in Table 1.

On the day after the addition of bromocriptine, the CPK level halved, rigidity disappeared, and body temperature returned to normal. In other laboratory examinations for the same day, following the continued increase in the patient's liver enzymes, urea and creatinine levels, and decrease in her urination, a diagnosis of acute renal failure was made. Fluid replacement and

bromocriptine treatment were continued for two more weeks – three weeks in total – and laboratory examinations returned to normal after the treatment.

DISCUSSION AND CONCLUSION

It is stressed in the literature that NMS occurs less often among the mentally retarded population (6). Severe liver failure in NMS is also reported very rarely in the literature. In one such case, a schizophrenic patient with long-term antipsychotic use, a diagnosis of NMS was made upon development of first ileus, then fever, rigidity, confusion, tachycardia, and hypotension and remission was reported with bromocriptine. After the use of antipsychotics, similar symptoms and severe liver failure developed again five years later, and were again treated successfully with bromocriptine (7). In our case, although severe liver and renal failure developed, the syndrome remitted completely with treatment.

Risk factors for NMS include a history of NMS, dehydration, hyperactivity, agitation, polypharmacy, antipsychotic dose, and the type, rate, and method of use (parenteral use) (1,2). In NMS, pathologies were detected with a 43 percent success rate with brain tomography and it was claimed that organic reasons could increase the likelihood of NMS. The relation between central nervous system damage in the base and the likely development of permanent neuropsychiatric sequellaes after treatment for NMS has also been noted (1).

The risk of developing NMS is accepted to be high in the first two-week period following a change to the dose of antipsychotic drug or the drug itself. In particular, the combination of long-acting antipsychotics with other psychotics can heighten the risk. In our case, following the initial hyperactivity and excitation, the antipsychotic treatment was altered, and the patient's high-dose, high-potency, long-term combination antipsychotic treatment was supplemented with another, parenteral antipsychotic shortly before depot treatment. Zuclopenthixol can be considered to have played a play a role in the development of NMS. In the literature, it was reported that a young schizophrenic patient with early onset developed NMS 48 hours after the addition of fluphenazine decanoate IM to the long-term thioridazine and haloperidol treatment he was following due to the development of aggression, similar to our case (8). In another case, NMS developed following the administration of 30 mg haloperidol IV in addition to 200 mg IV diazepam in 24 hours because of delirium tremens, and this was reported to have been treated with clonazepam and bromocriptine (3). In four other cases reported by Kasantikul and Kanchanatawan, following the long-term (one year) use of antipsychotic similar to our case, one of the cases developed NMS with bupropion (300 mg/day) (3). No chronic fever was observed in our case. A case of NMS with no fever was reported in the literature (9).

Clinicians must be careful with regard to this rare but potentially fatal side effect of antipsychotic treatment. It must be taken into consideration that the use of mainly parenteral, multiple, high-dose and in particular high-potency antipsychotics can increase the risk of NMS. Potential risks must be evaluated properly in the selection of antipsychotic after the occurrence of NMS.

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