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A Serious Side Effect of Antipsychotic Therapy: Neuroleptic Malign Syndrome

Antipsikotik İlaçların Ciddi Bir Yan Etkisi: Nöroleptik Malign Sendrom

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ABSTRACT

Neuroleptic malign syndrome (NMS) is a rare, idiosyncratic, potentially life-threatening complication of treatment with dopamine receptor antagonists. NMS is characterized by fever, severe muscle rigidity and autonomic and mental status changes. Here, we present three NMS cases admitted to our emergency service between January 2010 and April 2011. NMS has the characteristics of acute onset, hyperthermia, profound mental changes, heightened motor activity and autonomic symptoms. Aggressive and timely intervention is crucial due to the potential for fatal outcomes. Immediate withdrawal of the offending agent followed by supportive care is the treatment of choice for most patients. Supportive care includes the infusion of intravenous fluids for hydration and treatment with benzodiazepines to manage irritation.

Keywords: Antipsychotics, adverse effect, neuroleptic malign syndrome
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ÖZET

Nöroleptik Malign Sendrom (NMS) dopamin reseptör antagonistleri ile tedavinin nadir, idiosenkratik, potansiyel olarak hayatı tehdit edici bir komplikasyonudur. NMS ateş, ciddi kas rijiditesi ve otonomik ve mental durum değişiklikleri karakterizedir. Bu yazıda Ocak 2010 ve Nisan 2011 tarihleri arasında acil servisimize başvurmuş ve NMS tanısı almış 3 olgu sunulmaktadır. NMS akut başlangıç, hipertermi, belirgin mental değişiklik, artmış motor aktivite ve otonomik semptomlar ile ortaya çıkar. Agresif ve zamanında yapılan girişimler fatal sonuç potansiyeli açısından çok önemlidir. Kullanılan ajanın hemen kesilmesini takiben destekleyici tedavi çoğu olguda tercih edilen tedavi seçeneğidir. Destek tedavi, intravenöz sıvılar ile hidrasyonun sağlanması ve irritasyon için benzodiazepinlerin kullanımını içerir.

Anahtar Kelimeler: Antipsikotikler, yan etki, nöroleptik malign sendrom
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Introduction

Neuroleptic malign syndrome (NMS) is a rare, idiosyncratic, potentially life-threatening complication known to occur primarily during therapy with dopamine receptor antagonists such as antipsychotics (1, 2). However, NMS has also been associated with the use of a few antinausea agents, other drugs that affect central dopaminergic neurotransmission, and even by sudden discontinuation of antiparkinsonian medications (3-5). The incidence of NMS has been reported as being in decline from 3% to 0.01-0.02% in the recent literature (1).

We present three cases of NMS admitted to our emergency department (ED) between January 2010 and April 2011. We also discuss NMS in the context of the recent literature.

Case Reports

A diagnosis of "NMS was searched through ourhospital database system and three patients were found and evaluated retrospectively. Our first patient was a 51-year-old woman who had stopped talking with anyone and had not eaten anything for a week. She also exhibited body contractions. She had been prescribed sertraline hydrochloride 100 mg/day, paroxetine

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hydrochloride 30 mg/day and bornaprine hydrochloride 8 mg/day. She had altered mental status, generalized rigidity and urinary incontinence at the ED. Her drugs were discontinued and intravenous fluid replacement and lorezepam 5 mg/day perorally were applied in the observation unit of the ED. Her lumbar punture results were negative. Her mental status, muscular rigidity and agitation began to improve and she was admitted to the pscyhiatry unit on thirth day of follow-up at the ED.

Our second patient was a 23-year-old man who presented with decreased oral intake, nausea and vomitting. He had been prescribed clozapine 125 mg/day, quetiapine 150 mg/day and chlorpromazine 100 mg/day. However, there was a misunderstanding about dosing with clozapine such that his relatives had given him 100 mg pills instead of 25 mg for the four previous days. He was drowsy but did not have clear rigidity. Her drugs were discontinued and fluid replacement and ceftriaxone 2 mg/day intravenously and bromocriptine 2.5 mg/day perorally were applied in the observation unit of the ED. His mental status and vomitting began to improve and he was admitted to the pscyhiatry unit on the sixth day of follow-up at the ED.

Our third patient was a 47-year-old man who had complained of drinking too much water and excessive urination, diaphoresis and altered mental status. He had been prescribed quetiapine 400 mg/day, amisulpride 200 mg/day, zuchlopenthixol and risperidone in depot forms. His drugs were discontinued and he was admitted to the neurology unit after his diagnosis. All patients had altered mental status and diaphoresis, leukocytosis (11.8, 19.6 and 13.75 K/UL respectively; normal range (NR): 4-10), high values of creatinine kinase (CK) (9463, 13449 and 43079 U/L, respectively; NR: male 49-397, female 38-324) and lactic acid dehydrogenase (LDH) (594, 348 and 1175 U/L, respectively; NR: 98-192). Fever was also seen with patients 1 and 2, abnormally high blood pressure with patient 2 and urinary incontinence with patient 2 and 3 (Table 1). Patients 2 and 3 had high values of aspartate aminotransferase (AST) (84, 158 U/L, respectively; NR: 15-41). Patient 3 had a high myoglobin value >4000 ng/mL (NR: 17.4-105).

Discussion

NMS is typically characterized by the tetrad of fever, muscular rigidity, autonomic dysfunction and altered mental status (including lethargy, agitation, mutism or coma). However, clinicians should be bear in mind that although NMS is striking in its classic form, the condition is heterogeneous in terms of onset, presentation, progression and outcome, as in our cases. Common laboratory abnormalities include elevated creatine kinase levels, leukocytosis, elevated

Table 1. Clinical features and diagnostic evaluation of patients.

Psychiatric disorders history:				Patient 1 Psychosis + Panic disorder	Patient 2 Schizoaffective disorder	Patient 3 Schizoaffective disorder
Therapy with dopamine antagonist:				No	Yes	Yes
Withdrawal of dopamine agonist:				No	No	No
Therapy with selective serotonin reuptake inhibitors:				Yes	No	No
DIAGNOSTIC EVALUTION						
Levenson*		American Psychiatric Association*				
Major Criteria 1	Fever	Major Criteria 1	Fever	Yes	Yes	No
Major Criteria 2	Muscle rigidity	Major Criteria 2	Muscle rigidity	Yes	No	Yes
Major Criteria 3	Elevated CK level		Elevated CK level	Yes	Yes	Yes
Altered mental status		Altered mental Status		Yes	Yes	Yes
Tachycardia		Tachycardia		No	No	Yes
Leukocytosis		Leukocytosis		Yes	Yes	Yes
Diaphoresis		Diaphoresis		Yes	Yes	Yes
Abnormal blood pressure				No	Yes	No
Tachypnea				No	No	No
		Labile blood pressure		No	No	No
		Dysphagia		No	No	No
		Tremor		No	No	No
		Incontinence		Yes	No	Yes
		Mutism		No	No	No

*According to the American Psychiatric Association, diagnosis requires both major and at least two minor criteria, whereas all three major criteria or two major and four minor criteria must be present according to Levenson et al. (7, 8)

levels of hepatic transaminases and lactic acid dehydrogenase, hypernatremia or hyponatremia, metabolic acidosis, myoglobinuria, elevated blood urea nitrogen and creatinine levels and decreased serum iron levels. However, these laboratory findings are not specific. Cerebrospinal fluid analysis are normal in more than 95% of cases. Findings of neuroimaging studies are generally within normal limits and electroencephalography may demonstrate generalized slowing consistent with metabolic encephalopathy (1).

Differential diagnosis is of prime importance because NMS is a diagnosis of exclusion. It includes the following: CNS infections, idiopathic malignant catatonia, agitated delirium, benign extrapyramidal side effects, non-convulsive status epilepticus, malignant hyperthermia, thyrotoxic storm, pheochromocytoma, heat stroke, serotonin syndrome as well as drug overdose with phencyclidine, ecstasy, cocaine or amphetamine use (1, 2, 5).

The factors for increased risk of NMS have been reported as following: rapid increase in the dosage of antipsychotics, dehydration, psychomotor agitation, intramuscular application of antipsychotics, organic brain damage (IVC, Parkinson and Wilson's disease, addicts), fixation over a longer period of time, male gender, younger age (under the age of 50 years), concomitant administration of antipsychotics and abrupt discontinuation of anticholinergic medications (2, 3, 6).

The main causative factor is assumed to be dopamine hypofunction in NMS supported by our patients 1 and 3 (1, 2, 5). However, Steele et al. have claimed that the extreme clinical symptoms associated with NMS may not be totally explained by a simple decrease in central dopamine function, and multiple monoamines may be responsible for abnormalities, accounting for both NMS and serotonin syndrome (SS). They queried whether NMS and SS are the same. Atypical antipsychotics are able to increase dopamine release in certain areas of the brain by blocking serotonin 5-HT2a receptors. 5-HT2a receptors are expressed on the axonal terminal of dopaminergic neurons and their stimulation by serotonin causes a decline in dopamine release. The antagonizing effect of atypical antipsychotics prevent serotonin from diminishing the release of dopamine in which this enabled diminishing some side effects such as elevated prolactin, extrapyramidal side effects (EPSEs) and cognitive decline. Serotonin boosting drugs like serotonin reuptake inhibitors, tricyclic antidepressants and so on are known to cause EPSEs. The most likely mechanism for EPSEs is the stimulation of those same 5-HT2a receptors by increased intrasynaptic serotonin availability. The consequence of excessive serotonin stimulation of 5-HT2a activity on dopaminergic neurons is a diminution of dopamine release from dopaminergic neurons (3). This theory can explain why our patient 1, taking only SSRIs and no antipsychotics, had NMS.

The number of lethal outcomes among patients with NMS has significantly decreased, from 25% prior to 1984, to 7-11% in recent years due to timely detection of the initial symptoms and immediate therapeutic procedures (2). Discontinuation of antipsychotics as well as of other psycho-pharmaceuticals should be the first intervention. Administration of a dopamine agonist, bromocriptine or amantadine, is recommended and the application of dantrolene in hyperpyrexia, as well as volume replacement, acidosis and hypokalemia correction, combined with the treatment of complications due to rhabdomyolysis is effective. Broad spectrum antibiotics, heparin for the prevention of disseminated intravascular coagulation and pulmonary embolism, as well as benzodiazepines, and if necessary, electroconvulsive therapy have also been used (1, 2). Sato et al. stated that methylprednisolone shortened the illness duration of NMS in Parkinson's Disease and laboratory values within 10 days (4). Intensive medical care should include careful monitoring for complications, including cardiorespiratory failure, renal failure, aspiration pneumonia and coagulopathies, and may involve support of cardiac, respiratory and renal functions (1). Our patients did not develop any complications during their stay at the ED.

After the withdrawal of all NMS symptoms, antipsychotic agents should be discontinued for at least two weeks. During the wash-out period, the following agents can be used: clonazepam, lorezapam, mood elevators if necessary and antipsychotic agents with a different mechanism of action (clozapine or olanzapine) with low affinity for dopamine receptors. Depot preparations are excluded from therapy (2).

Conclusion

Emergency physicians should be familiar with all the side effects of antipsychotic therapy, because a timely intervention can prevent the complete clinical manifestation of NMS and its complications. On other hand, whenever providing medication, especially high-potency antipsychotics for an agitated patient in the emergency room, the emergency physician must ensure careful scrutiny of the patient.

Conflict of interest

No conflict of interest was declared by the authors.

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