Neuroleptic Malignant Syndrome: A Case Treated With Bromocriptine

ÖZET
Nöroleptik malign sendrom: Bromokriptin ile tedavi edilen bir olgu
Nöroleptik malign sendrom (NMS), özellikle antipsikotik tedavi esnasında nadir olarak görülen ve potansiyel olarak ölümü olabilen bir sendromdur. Bu yazida, hastanede uzun süre tedavi altında bulunan, uzun yıllar antipsikotik kullanımı ve birçok kez yatışları olan, şizoaffektif bozukluk tanısıyla izlenen bir olguda, oral ve depo antipsikotik ilaç tedavisinde yapılan doz artırmının ardından gelişen NMS ve ona yönelik tedavi yaklaşımı sunularak NMS tedavisinde bromokriptin kullanımı tartışılınır.

Anahtar kelimeler: Nöroleptik malign sendrom, antipsikotikler, bromokriptin

INTRODUCTION
Neuroleptic malignant syndrome (NMS) is a potentially fatal syndrome seen rarely during treatment with antipsychotic medications (1). The prevalence of NMS is reported as 0.01 to 3 percent in different studies (1-4). Its etiology is not entirely known but is considered to be idiosyncratic. NMS can potentially manifest in all patients using antipsychotics. This risk is independent of the period of use of the drug (1). The syndrome is characterized by findings such as dimness of consciousness, autonomic dysfunction, muscular rigidity, and hyperthermia (2,3). Its differential diagnosis from such conditions as malignant hyperthermia and lethal catatonia manifesting with fever is very important. Early diagnosis and treatment is vital. The mortality rate varies in numerous sources, but is generally around 10 percent (3). Dopaminergic blockage is believed to part of the mechanism of NMS. Animal trials and the usefulness of agonist agents such as bromocriptine and amantadine in treatment support this view (1-3).

A review paper written by Pelonero et al. (4) in 1998, which included cases between 1960 and 1997, emphasized that the differential diagnosis of NMS must be made in all patients with fever, rigidity, and maintenance antipsychotic treatment. Although there are still contradicting opinions on specific drug treatments, there is a consensus on the administration of intravenous (IV) fluid replacement to correct antipyretic, cooling, dehydration, and electrolyte imbalance (3,4). The majority of patients recover within two to 14 days without any cognitive deficit. In patients with manifestation of cognitive disorder, fever, hypoxia and other complications are considered to be responsible for this condition (4).

In this paper, we discuss the development of NMS in a patient who was followed with schizoaffective disorder diagnosis, had received treatment in our clinic and used antipsychotics for many years, and had hospitalized many times. NMS developed after increasing dose of oral and depot antipsychotics. We also present the treatment approach used for NMS and the use of bromocriptine in the treatment of NMS.

CASE
The patient is a single 40-year-old male, primary school graduate, with history of 35 hospitalization in...
our hospital between 1989 and 2010. Total duration of hospitalizations is 94 months. He has been treated with various oral and depot antipsychotics during this period. The patient did not use antipsychotics regularly when he was out of the hospital and repeatedly committed crimes. His latest hospitalization was under the protection and treatment decision of the court.

The patient is followed with diagnosis of schizoaffective disorder, was found to have not used any drugs for four months. His disease was in relapse. His treatment was set as risperidone 4 to 6 mg/day, chlorpromazine 600 mg/day, sodium valproate 1000 mg/day, biperiden 2 mg/day, and fluphenazine decanoate 25 mg/15 days. One week later, quetiapine 600 mg/day was started to replace risperidone, afterwards, the dose was raised to 900 mg/day. Three weeks later, quetiapine was replaced with sulpiride 600 mg/day and the chlorpromazine dose was increased to 700 mg/day.

On the 10th day after the change in treatment, the patient mentioned complaints of pain in his muscles, drowsiness, imbalance and spasms, urinary continence, and rectal bleeding during the previous night. In his examination, we observed a distinct decrease in his psychomotor activity, as well as anteflexion posture, and rigidity and cogwheel phenomenon in his extremities. His body temperature was 37.5°C, pulse 76/min., blood pressure 140/90 mmHg. In laboratory examinations made on the same day, the leucocyte count was 17,700 10^3/µL, chlorine 93 mmol/L (95-110) low, RBC 4070 10^3/µL, Hb 12.7 g/dL, Hct 38.7 percent and iron (Fe) 10 ug/dL, CPK 2185 IU/L, chlorine 94 mmol/L (95-110), and sodium 133 mmol/L (135-145). No features were detected in his urine tests. In the follow-up, body temperature was 37°C, 39.5°C and 37.5°C, pulse 110/min., 120/min., and blood pressure 100/60 mmHg-140/80 mmHg. The patient, whose rigidity and cogwheel phenomenon symptoms continued, was sedated. Neck stiffness was not observed. There were fluctuations in the autonomous nervous system findings. Bromocriptine 15 mg/day was added to his treatment with the diagnosis of NMS. Antipyretic and IV fluid replacement were continued. Anal fissure was detected in the general surgery consultation on the second day, oral antibiotic treatment was prescribed, anemia was diagnosed with internal medicine consultation and iron replacement was started. In laboratory tests, the leucocyte count was 14,500 10^3/µL (neutrophil 82 percent), RBC 3490/µL, Hb 11 g/dL, Hct 33.1 percent; CPK 1779 IU/L, chlorine 93 mmol/L (95-110), and sodium 129 mmol/L (135-145). On the third day, a lung graph was done and no pathology was detected. In laboratory tests made on the fourth day of follow-up, the leucocyte level was 14,700 10^3/µL (neutrophil 81 percent), RBC 3720 10^3/µL, Hb 11.8 g/dL, Hct 33.9 percent; CPK 622 IU/L, SGPT 53 IU/L (5-60), SGOT 77 IU/L (10-50), LDH 216 IU/L (90-200), chlorine 99 mmol/L (95-110), and sodium 136 mmol/L (135-145). His electrolytes were within normal limits and his liver enzymes were on the rise. Iron was 30 ug/dL. On the fourth day of bromocriptine use, CPK decreased to normal limits with 234 IU/L (25-250). In repeated tests, the leucocyte count was normal on the 10th day. Liver enzymes (SGOT, SGPT, LDH) were within normal limits by the end of the third week. High CPK is related to rhabdomyolysis and liable to cause renal failure. No renal complications occurred in our case.

Bromocriptine was decreased to 10 mg/day one week later, and discontinued in the third week. As of the second day of bromocriptine treatment, autonomous findings improved, CPK values decreased and did not rise again. In examinations, anteflexion posture, rigidity and cogwheel were reduced but continued. The patient did not have any remaining complaints, other than...
pain in the legs. The longest continuing symptoms were anteflexion posture and cogwheel phenomenon. In an evaluation of the patient one month later, extrapyramidal findings had also resolved. The patient recovered without complications. His treatment with clozapine was continued, 25 mg/day was started on day 25. Except for very short absences, he has been treated in our hospital for the last four years. The patient did not develop NMS again, and his treatment was occasionally supplemented with zuclopenthixol depot. His treatment has been continued with 200 to 500 mg/day clozapine for a year without complications.

DISCUSSION

NMS was first reported in 1954 by Delay and Deniker and first defined in 1960 (1,5). NMS can be encountered in all diagnostic groups. Organic reasons increase the risk. It can manifest in Parkinson’s patients upon discontinuation of dopamine agonists, in Huntington’s patients after starting tetrabenazine, and during the use of all antipsychotics, antiemetics, (perphenazine and metoclopramide), serotonin reuptake inhibitors (SSRI), lithium, and in particular fluoxetine (1, 4). The risk intensifies in the first two days of antipsychotic treatment and in periods when doses are increased. The risk also is also higher in young males, those with high dose and parenteral drug use, those with low functional dopamine receptor count, in those with decreased serum iron, and in previous NMS patients. Dehydration, utter exhaustion, depot antipsychotic use, extrapyramidal syndrome (EPS) resistant to treatment, and alcohol use are other factors that increase the risk of NMS (1,3,4). Although major and minor criteria are suggested in the diagnosis of NMS, the diagnosis is made clinically and the differential diagnosis is of vital importance. Levenson suggested the major and minor criteria in 1985 and changed these in 1986 (1,5,6). He identified fever and rigidity as major criteria and considered high CPK as major criterion only when it is 100 times greater. A decrease in CPK is determinant that represents the end of the syndrome. Similarly to another case reported in 1998, CPK can be within normal limits alongside NMS findings (7). In addition to CPK and blood count, it is vitally important to make urine examinations and advanced examinations like electrolytes, calcium, magnesium, kidney, thyroid and liver function tests, lumbar puncture, EEG, BT, and MRI to determine etiology when necessary (1,3,5). In this high-mortality syndrome, mortality rises in the presence of myoglobinuria. Neurological sequelae and dementia may be permanent in severe cases (4).

In our case, major and minor criteria for NMS were present, and male gender, use of depot antipsychotic, recent drug change and dose increase, and presence of iron deficiency were considered risk-increasing factors (4).

In the differential diagnosis, our patient’s progress was stabilized with antipsychotic use. After we detected NMS, we moved away from lethal catatonia. Anesthesia was not administered to our patient, which caused us to exclude the diagnosis of malign hyperthermia. Neither did we have any clinical observations suggesting anticholinergic intoxication.

The literature points out that seven of the 11 reported cases of NMS with risperidone were below the age of 65 (8,9) and that NMS began within 12 hours to 23 days of the start of risperidone treatment in these cases (8). As in our case, patients with depot antipsychotics (zuclopenthixol deconoate depot and fluphenazine deconoate depot) in their treatment were reported as well (10-12).

The general principle of the treatment is stopping antipsychotic treatment and starting symptomatic treatment (hydration with IV fluids, controlling fever with antipyretics and external cooling) as a life-saving measure. Many authors suggest a trial of treatment with bromocriptine, dantrolene, amantadine, and combinations of these. Studies on this subject have reported conflicting results about the usefulness of the above-mentioned drugs (6). There are studies indicating that bromocriptine, a dopamine agonist, is useful in treatment and shortens the recovery time (13-15). A case report by Zubenko and Pope (13) states that a 24-year-old patient diagnosed with schizoaffective disorder who developed NMS after administration of fluphenazine deconoate depot and did not benefit from amantadine responded dramatically to bromocriptine.
after the second dose. The clinical findings of this case and his good response to bromocriptine are similar to our case. Azorin et al. stated that starting bromocriptine immediately after the onset of symptoms is quite important in treatment (14). Another study reveals that of two reported NMS cases, one was treated in intensive care with supporting treatment and the other in the inpatient unit with bromocriptine. The latter case was treated with bromocriptine on day 10, having not responded to other drugs earlier on, and started to improve rapidly two hours later, improved more distinctly when the dose was raised to 30 mg day, and did not have any remaining findings except for minimal EPS symptoms three weeks later (15). A case report by Tomruk et al. (16) states that the patient manifested NMS after the long-term administration of fluphenazine deconoate depot and haloperidol. After bromocriptine treatment was administered with supporting treatment, there was a rapid drop in CPK level and fever, and decrease in rigidity, and the patient recovered completely in three weeks. A study conducted by Rosebush et al. (5) showed that 34 of 37 NMS cases responded well to bromocriptine and recovered in 10 days on average, and that the recovery was quick. Tural and Önder (17) state in their study evaluating NMS cases published in Turkey between 1985 and 2005 that bromocriptine was used in 20 of the 36 total NMS cases, that combination treatment was administered in 11 of these cases and only two cases who received bromocriptine died. Our case also recovered without any deficits and in clinical conditions with supportive therapy and bromocriptine, and did not require intensive care. Furthermore, there was no relapse in his psychiatric condition. Along with symptomatic treatment, cases recovering with combined treatment including ECT were also reported (17,18). A screening study (including 271 cases) about dantrolene, drug not available in Turkey, did not produce evidence that dantrolene is more effective than other treatments and decreases mortality (19). It has been suggested that the difference in results of case reports could be due to properties of the antipsychotics causing the syndrome, duration until treatment of NMS, and age of the patient.

**CONCLUSION**

We are of the opinion that the good response of our patient to treatment and his recovery without any deficits largely resulted from quickly establishing diagnosis, discontinuing antipsychotic drugs and starting supporting treatment and bromocriptine after his complaints, scanning for other organic disorders in detail, and starting treatment for iron deficiency immediately. We believe that in patients with potential NMS in whom hypothermia is detected following the administration of an antipsychotic, first the leucocyte count should be taken, CPK measured, arterial blood pressure tracked (in line with the literature), and then bromocriptine should be started quickly, along with symptomatic treatment, as a lifesaving measure.

**REFERENCES**

Neuroleptic malignant syndrome: a case treated with bromocriptine