NÖROLEPTİK MALİGN SENDROM

THE NEUROLEPTIC MALIGNANT SYNDROME

Yılmaz Niyazi YAZMAN, İbrahim İYİGÜN

Atatürk Üniversitesi Tıp Fakültesi Nöroloji Anabilim Dalı, Erzurum

Özet

Nöroleptik malign sendrom (NMS) özellikle haloperidol gibi nöroleptik alan hastaların yaklaşık olarak %1'inde oluşur ve potansiyel olarak öldürücüdür. Bu yazıda 39 °C'ye kadar yükselen ateş, belirgin rijidite, taşikardi ve şuur bozukluğu olan bir vaka sunulmuş ve NMS'nin klinik prezentasyonu, tedavisi ve prognozu literatür bilgileri eşliğinde gözden geçirilmiştir.

Anahtar kelimeler: *Nöroleptik malign sendrom, Bromokriptin, Prognoz*

Summary

Neuroleptic Malignant Syndrome (NMS) may occur at any time during the course of therapy in as many as 1 percent of persons who take neuroleptics, particulary haloperidol. In this paper, one case with fever (as high as 39 °C), marked rigidity, tachycardia and consciousness is presented, and clinical presentation, treatment and prognosis of NMS is discussed.

Key words: *Neuroleptic malignant syndrome, Bromocriptine, Prognosis*

Introduction

Neuroleptic malignant syndrome (NMS) is a rarely seen clinical picture characterised by leukocytosis, high creatine phosphokinase (CPK), conscious disorder showing fluctuation, autonomic dysfunction, extrapyramidal symptoms, hyperthermia appearing as a complication of the antipsychotic (AP) medicines (1-2). Pathogenesy is not known definitely. Mortality rate is approximately 20% (1-2).

Case 1

An eighteen year old male patient was brought to our clinic from State Hospital because of conscious disorder, rigidity, high fever and sweating. It is learnt that the patient, which had no complaints before, had agitations for are week. It's learnt that 5 mg of haloperidol, 5 mg of biperidine lactate and 25 mg of chlorpromazine i.m. were injected to the patient having the diagnosis of acute psychotic attack and this was repeated 4 hours and 24 hours later and high fever, sweating conscious disorder, opustotonus and rigidity developed and then 5 mg of biperidine lactate i.m. was applied and no healing occured in the syptpms. The general picture of the patient was bad, Glasgow Coma Scala (GCS) score: 11, Blood pressure (BP):120/80 mmHg, Pulse rate (PR): 110/min (rythmic), Fever: 39°C, Respiratory rate (RR): 28/min. His skin was pale and sweaty. Axial and limb tone was markedly increased. The patient was in opustotonus position. There was urine incontinence. There was no other neurodeficit. When BUN:63 mg/dl, creatinin=3.0 mg/dl, CPK: 4713 IU/l (n: 10-190 IU/L); other routine biochemical tests, hemogram, erythocyte sedimentation speed (ESS) and cerebrospinal fluid (CSF) inspections were normal. There was no reproduction in blood, urine, throat and CSF cultures. Tyroid function tests (TFT), chest radiogram, electroencephalogram (EEG) and computed tomography (CT) were evaluated as normal. AP medicines were interrupted. In addition to the supportive treatment, 5 mg/day of biperidine lactate i.m. was contunued to apply, but it was not successful. At the third day; Fever:39°C, PR: 130/min, CPK:4560 IU/L. Tracheotomy was applied to the patient having breathing problem. Bromocriptine of 7.5 mg/day (parlodel 2.5 mg 3õ1, Novartis) was begun to be given by nazogastric way. Treatment continued in the intensive Care Unit. Dose was increased until clinical response was held and it was reached to the 22.5 mg/day. At the third day of bromocriptine treatment the patient was afebrile and CPK was 210 IU/L. At the 5th day the conscious and the muscle tonicity healed apparently. At the 7th day; GCS score:15, BUN: 17 mg/dl, Creatinin: 0.8 mg/dl and CPK= 180 IU/L. The patient was discharged at the eleventh day his enterance.

Case 2

A 28 year old male patient was brought to our clinic with the complaints of attacking to his environment, concious unclearity, harshness in his muscles, high fever and sweating. It's learnt that the patient suddenly began to have aggressive behaviours fifteen days ago and he had no complaint before that. 25 mg of fluphenazine decanoate was injected and 2 mg/day of haloperidol and 100 mg/day of thioridazine HCL was given orally to the patient by a doctor. At the 15th day fluphenazine decanoate was repeated in 25 mg i.m. and his conscious became unclear the day after. The general picture of the patient was bad, GCS score: 12, the skin was pale and sweaty. BP:200/110mmHg, PR:110/min (rythmic), Fever:39°C and RR:24/min. Prevalent rigidity and tremor were observed in the muscles. There was also urine incontinence. In laboratory investigations; CPK was 1032 IU/L and White blood cells (WBC) was 21900/mm³, the other routine biochemical tests, hemogram, ESS, TFT, urine and CSF were normal. Chest radiogram, EEG and CT were evaluated as normal. There was no reproduction in blood, urine, throat and CSF cultures. AP medicines were interrupted. 20 mg/day p.o. (parlodel 2.5mg 4õ2, Novartis) of bromocriptine was began. In the eighth hour of the treatment, when BP was 120/60 mmHg and fever was 36.5°C and WBC was 13500/mm³, the consciousness intended to sleep and rigidity and tremor was continuing. CPK was 1142 IU/l. At the second day; the conscious was open but sometimes there were agitations. Fever=36.5°C, PR:88/min., CPK:669 IU/L, WBC:10800/mm³. At the 5th day, the patient was afebrile and conscious. Vital findings were stable and rigidity and tremor were diminishing. CPK:230 IU/L. At the 19th day the patient was discharged.

Discussion

NMS may appear in every time in 0.5-1% of the patients which had antipsychotic treatment. Although it is stated that it may appear after first dose or 5-10 days

after the medicine was quited; it is known that it appears between the 24-72 hours of the treatment and in the theraupatic doses rather than the toxic doses (1-2). Syndrome developed in theraupatic doses in both of the patients. Syndrome developed at the third day of the AP treatment in the first patient, it developed at the 16th day in the second. In seperative diagnosis; the infections of central nerve system, heat stroke, malign hyperthermia (MH), lethal catatonia (LC), lithium intoxication, central anticholinerjic syndrome, acinetic mutism, serotonin syndrome, hyperparatyrodism, tetanos, stricnin intoxication, locked in syndrome and tyrotoxicose will be taken into account (2-4). We did not determine a pathology supporting the central nerve system infection in both of the patients. It's important in seperative diagnosis that skin is dry and there's no rigidity and other extrapyramidal findings in heat struck (2-3). MH is an hereditary clinical picture charaterised by serious muscle contractions and sudden increase in body heat resulting from being subject to some agents like succinylcolin and inhalation anesthetics (5). LC resembles NMS clinically and mostly it can't be seperated. It's been accepted that NMS is a form of catatonia and not a different entity (6). For the reasons that NMS is seen after the usage of AP agents blocking dopamine receptors and hyperthermia and extrapyramidal symptoms are the ongoing symptoms; dopaminergic hypoactivity in hypothalamus and striatum gaired importance (1,3,7). A lot of agents cause NMS besides the AP medicines. The sudden interruption of the antiparkinsonien medicines like L-dopa and karbidopa, and the medicines utulizing dopamine like tetrabenazine and a- methyl-tyrosine cause NMS (1-4,8). The reason of the disordered thermoregulation in NMS is the capture of hypothalamic and other lymbic dopamin receptors by the neuroleptic medicines (3). The succes of bromocriptine and amantadine, the agonist of dopamine, in NMS treatment supports this hypothesis (1-2,6-7). There are some studies showing the succes of carbamazepine in treatment by effecting dopamine activity in hypothalamus or making gamma-aminobutiric acide regulation (9). For the reason that NMS and MH resemble each other; dantrolene sodium which is successful in MH treatment is experienced in NMS treatment (2,7,10). Hyperthermia in MH is related to the heat produced by muscle activation and dantrolene sodium effects muscle directly and blocks heat production and muscle relaxation successfully (5). Tsujimato et al (10) expressed that they used high dose dantrolene with hemodialisis in a NMS case having acute renal insufficiency and they gained success. Granato et al (7) used dantrolen sodium in the treatment of a NMS case and at 12th hour fever, at the 48th hour serum CPK levels were decreased to normal levels. However, there was no healing in rigidity and tremor. At the 8th day, they began to give bromocriptine and at the second day of the bromocriptine treatment, they observed that muscle tonus and tremor healed. Although muscle relaxation is obtained by several methods in the previous studies, fever couldn't be decreased and this made us think that hyperthermia is central origined (1). NMS is rare but a life-threatening clinical picture. For this reason thinking about NMS in seperative diagnosis in every patient having complication when they are getting AP treatment, and the usage of dopamine agonist agents in addition to the supportive treatment; we believe that mortality rate will decrease.

References

1. Smego RA, Durack DT. The neuroleptic malignant syndrome. Arch Intern Med 1982;142:1183-1185
2. Guze BH, Baxter LR. Current concepts. Neuroleptic malignant syndrome. N Eng J Med 1985;313:163-166
3. Henderson VW, Wooten GF. Neoroleptic malignant syndrome: a pathogenetic role for dopamine receptor blockade? Neurology 1981;31:132-137
4. König F, Löble M, Wolfersdorf M. Depressiver stupor-malignes neuroleptisches syndrom-serotoninsyndrom; ein kasuistischer beitrag zu einer schwierigen differentialdiagnose. Nervenartz 1996;67:407-412
5. Gronert GA. Malignant hypertermia. Anesthesiology 1980;53:395-423
6. Topka H, Buchkremer G. Katatonie, malignes neuroleptisches syndrom und myositis ossificans. Nervenartz 1996;67:413-417
7. Granato JE, Stern BJ, Ringel A, et al. Neuroleptic malignant syndrome: sucessful treatment with dantrolene and bromocriptine. Ann Neurol 1983;14:89-90
8. Burke RE, Fahn S, Mayeux R, et al. Neuroleptic malignant syndrome caused by dopamine-depleting drugs in a patient with Huntington disease. Neurology 1981;31:1022-1026
9. Thomas P, Maron M, Rascle C, et al. Carbamazepine in the treatment of neuroleptic malignant syndrome. Biol Psychiatry 1998;43:303-305
10. Tsujimoto S, Maeda K, Sugiyama T, et al. Efficacy of prolonged large-dose dantrolene for severe neuroleptic malignant syndrome. Anesth Analg 1998; 86: 1143-1144

Yazışma Adresi:
Dr. Yılmaz N. YAZMAN

Atatürk Üniversitesi Tıp Fakültesi
Nöroloji Anabilim Dalı, Erzurum

YORUM

Yazman ve İyigün bildirdikleri iki olgu ile nöroleptik malign sendroma (NMS) dikkat çekmektedir. NMS nöroleptik ilaçların seyrek görülen ciddi ve potansiyel olarak öldürücü bir reaksiyonudur. Hipertermi, otonomik disfonksiyon, ekstrapiramidal semptomlar ile

serum kreatinin kinazında (CK), özellikle MM bandında yükselme ve lökositoz ile karakterize olan bu tablo daha çok haloperidol, biperidin ve flufenazin alan olgularda tedavinin herhangi bir zamanında ortaya çıkabilmektedir (1,2). Etyolojisi aydınlatılmamış olmakla beraber santral dopaminerjik blokajın olduğu görüşü son zamanda kabul görmektedir (3). Yazman ve İyigün NMS 'nin ayırıcı tanısını iyi bir şekilde tartışmışlardır. Söylenenlere nöroleptiklerin serum CK düzeyini yükselttikleri ve bunun monitorizasyonunun gerekmediği (4), NMS 'nin hipertermi olmadan da görülebileceği (5), sağaltımda elektro konvülsif şok tedavisinin (6) de kullanılıp yararlı sonuçlar alınabildiği eklenebilir. Günümüzde nöroleptik kullanımının yaygınlaşmasının özellikle "mal practice" dikkate alındığında NMS olgularının görülme sıklığını artırabileceği beklenebilir.

Yüksek mortalite oranı göz önüne getirildiğinde bu bildiri aracılığıyla nöroleptik uygulamasının kesin endikasyonu olan olgularda kullanılması, gerekmedikçe kombinasyonlardan kaçınılması ve bu uygulamalar sırasında her zaman görülebileceğinden dolayı NMS 'un iyi tanınmasının gerektiği kanısındayım.

Kaynaklar

1. Pelonero AL, Levenson JL, Pandurangi AK. Neuroleptic malignant syndrome: a review. Psychiatr Serv 1998;49:1163-72
2. Velamoor VR. Neuroleptic malignant syndrome. Recognition, prevention and management. Drug Saf 1998;19:73-82
3. Jauss M, Krack P, Franz M, Klett R, Bauer R, Gallhofer B, Dorndorf W. Imaging of dopamine receptors with [123I]iodobenzamide single-photon emission-computed tomography in neuroleptic malignant syndrome. Mov Disord 1996;11:726-728
4. Meltzer HY, Cola PA, Parsa M. Marked elevations of serum creatine kinase activity associated with antipsychotic drug treatment. Neuropsychopharmacology 1996;15:395-405
5. Hynes AF, Vickar EL. Case study: neuroleptic malignant syndrome without pyrexia. J Am Acad Child Adolesc Psychiatry 1996; 35:959-962
6. McKinney P, Kellner C. Multiple ECT late in the course of neuroleptic malignant syndrome. Convuls Ther 1997;13:269-273

Dr. Hakan Hadi KADIOĞLU