Afebrile Neuroleptic Malignant Syndrome associated with Fluphenazine decanoate: A case report

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Neuroleptic Malignant Syndrome (NMS) is unusual but could be a lethal reaction associated with neuroleptic drugs. It occurs in almost 0.07-2.2% of patients under treatment with neuroleptics. There are some medical treatments that may also be helpful for its treatment, including dopamine agonists, muscle relaxants, and electroconvulsive therapy (ECT). We present this case to alert the clinicians to the potential for inducing afebrile NMS.

Our case is a 41-year-old man with a history of schizophrenia showing signs and symptoms in accordance with NMS, 2 weeks after receiving one dose of 12.5 mg fluphenazine decanoate, abruptly following the 3rdsession of ECT. The patient presented with decreased level of consciousness, muscular rigidity, waxy flexibility, mutism ,generalized tremor, sever diaphoresis and tachycardia which progressed during the previous 24 h. Laboratory data indicated primarily leukocytosis, an increasing level of creatinine phosphokinase and hypokalemia during the next 72h.

In patients receiving antipsychotics, any feature of NMS should carefully be evaluated whether it is usual or unusual particularly in patients receiving long acting neuroleptics.

Keywords: *Antipsychotics,Fever, Fluphenazine Neuroleptic malignant syndrome, Electroconvulsive therapy*

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Neuroleptic Malignant Syndrome (NMS) is a potentially serious complication that may occur anytime during the course of therapy with neuroleptics, which antagonize dopaminergic receptors in the nigrostriatal pathway. The symptoms include muscular rigidity, agitation, mutism, akinesia, severe hyperthermia, sweating and increased pulse and blood pressure resulting in cardiovascular collapse. Laboratory results comprise an increased white blood cell count and increased levels of creatinine phophokinase, liver enzymes, plasma myoglobin and myoglobinuria infrequently associated with renal failure. Fluphenazine decanoate is a long-acting depot anti-psychotic, and electro convulsive therapy is one of the most long-established treatments for psychiatric disorders in constant use (1). Although NMS is uncommon, it is a potentially critical reaction associated with neuroleptic drugs (2). According to more recent data, it occurs in roughly 0.01%-0.02% of patients treated with neuroleptics although it was previously supposed to be up to 3% (3). The probable risk factors of this syndrome are as follows: previous NMS episodes, confusion, disorganized behavior, psychomotor agitation, , dehydration, polypharmacy, and the rate and route of neuroleptic administration (4,5).

Some useful medical treatments for the treatment of NMS are dopamine agonists, muscle relaxants, amantadine and bromocrpitine. Electroconvulsive therapy (ECT) has been applied with favorable outcome by some clinical therapists (1).

In this report, because of unusual presentation of NMS without fever, we present a patient with signs and symptoms of NMS with no detection of hyperthermia.

Case Report

Our case is a 41-year-old man with a 4-year history of schizophrenia, presented with impaired cognition after 2 weeks of hospitalization in Meimanat mental hospital in Tehran. The patient had no report of fever in his early observation in which he was noted to have tachycardia, muscular rigidity, generalized tremors, mutism and diaphoresis.

He had already been under treatment with Lithium 900mg/24h ,clonazepam 1mg /hs, one intramuscular injection of 12.5mg fluphenazine decanoate once every other day 2 weeks before the presentation of NMS and three sessions of ECT (Electroconvulsive Therapy). ECT was applied due to his prominent positive symptoms of self talking, auditory hallucination and persecutory delusion. The presentation of NMS started just after the third session of ECT. Lithium had been discontinued a day prior to the beginning of ECT. He did not have any history of drug or food allergies. Initial vital signs showed a pulse rate of 134 beats/min, a blood pressure of 111/79 mmHg and axillary temperature of 37 (C). The patient's general muscular tone was rigid at first. His mucous membranes were

dry. Physical examination of both lungs revealed no abnormality, but the patient had sinus tachycardia with a regular rhythm. There were no acute findings or evidence of surgical scars in his abdominal examination. The only positive point in his medical history was an occurrence of deep venues thrombosis of the left leg 2 years earlier. The pulses in all four extremities were normal.

Laboratory assessment showed an initial serum creatinine phosphokinase level of 91 U/L. Leukocyte count was 12,1000/mm3 with a hemoglobin of 11.8 g% and a hematocrit accounted for 33%. The patient's serum sodium level was 141 mmol/L, potassium 3.8 mmol/L, blood urea nitrogen level 9 mg/dL, and creatinine stood at 0.8 mg/dL. Lumbar puncture evaluation was normal , and computed tumography (CT) of the brain was also performed which showed an old ischemic region in the left parietal lobe being asymptomatic and not clinically important.

Urine drug test did not show any proof of opiates, amphetamine, cocaine, cannabis tricyclic antidepressants, or barbiturate exposure.

The probability of neuroleptic malignant syndrome was considered, so therapy with fluphenazine and ECT was immediately discontinued. The renal output vital signs, electrolytes, and fluid balance were monitored. In order to overcome muscle rigidity and antipsychotic-induced dopamine receptor blockade the patient was given supportive medication: dantrolene and bromocriptine. For more supportive care, the patient was admitted to the intensive care unit. Over the first 24h of admission, the patient remained mute. On the second day of admission, although the patient's temperature was normal, his creatinine phosphokinase (CPK) levels increased to 2800U/L. Culture evaluation of all blood, urine, cerebrospinal fluid samples were negative for growth. By the second day, the patient got extremely agitated. He responded to NaValproate(600mg/day) and Lorazepam(3mg/day). On the 3rd day, CPK level escalated to 4880 U/L. A magnetic resonance scan of the brain showed an old ischemic region in the left parietal lobe without any acute pathologic process. An electroencephalogram did not show any noticeable abnormality. The patient was transferred from ICU to a regular ward on the 8th day of his admission when CPK level decreased to 1760 U/L.

The patient remained afebrile until the 8th day of admission when he began to show signs of steadily increasing temperature and diarrhea which was diagnosed as pseudo membranous colitis and was treated with Rifampin(450mg/day) and Metronidazole(750mg/day). His hospital courses were complicated by deep venous thrombosis (DVT) in the right leg which was detected by the right leg edema and sever pain. Dopler sonography showed left tibial vein thrombosis. Therapy with heparin started and followed by warfarin with control of PT after consulting with our cardiologist. DVT subsided after 5days. The patient was discharged after 15 days of hospitalization with a satisfactory general medical condition and normal mental status. He was then referred to a cardiologist for following up the therapy with wafarin which was recommended to be continued for a long time because of recurrent DVT.

Discussion

ECT is one of the considerable strategies for the treatment of NMS which has been addressed in many cases in the literature (6-8).

In the review of literature, we found occasional reporting of afebrile presentation of NMS. For example, Anelopoulos se al reported a 31-year-old Caucasian male who developed NMS and whose temperature was 37 throughout the episode and was treated with amisulpiride (800mg/day) for 2 years and oxcarbazepine (1200mg/day) for one month (9). Moreover, Lev and Clark stated a case of NMS with no initial onset of fever (10).

In our patient, one intramuscular dose of 12.5 mg fluphenazine followed by 3 sessions of ECT leading to extrapyramidal symptoms and mental status changes. This presentation was similar to observations reported previously by Aruna when a patient had been given 25 mg of fluphenazine decanoate injection intramuscularly in addition to his ordinary psychotropic treatment of thioridazine and haloperidol. Laboratory analysis indicated rising of creatine kinase, aspartate aminotransferase, alanine aminotransferase levels and leukocytosis (11).

In our case, symptoms began just after the 3rd session of ECT. In a case control study Shachdev, et al. stated that past history of treatment with ECT maybe considered as a risk factor for the development of NMS (12). On the contrary, we found articles reporting ECT as a useful measure to treat NMS (5-8).

Our patient did not have a persistent hyperthermia. We detected low grade fever only once upon the occurrence of developing diarrhea during his hospital admission which was considered as a result of dehydration.

It is not certain whether receiving 3 sessions of ECT have affected the course of NMS to be presented without fever in our case. Moreover, it was worth considering that in spite of therapy with ECT, our patient developed the symptoms of NMS.

Regarding the treatment of NMS, the clinicians should focus at supportive therapy and discontinuation of the precipitating drugs. The patient's intake and output should be seriously taken into consideration throughout the treatment course. Rehydration as a supportive action must be initiated to stabilize the patient's blood pressure. In order to lower the body temperature, cooling blankets, and muscle relaxants such as dantrolene and diazepam are useful in acute situations. Providing a satisfactory airway and ventilation are principal, especially when we confront neurologic deterioration. Following the discontinuation of the aberrant agent and suitable treatment measures, recovery usually occurs over 5 to 14 days (2, 13).

Conclusion

NMS is a life-threatening condition resulting from dopaminergic blockade from antipsychotic medications. In our patient, the actual assessment revealed that fluphenazine deaconate was the probable cause of NMS. However, it remains uncertain whether alteration in other neurotransmitter systems besides dopamine caused by ECT could be involved in afebrile staging of NMS in this patient. We should be aware of this drug-induced condition and the likely increased risk associated with concurrent use of ECT and long-acting psychotropic drugs.

In patients taking any antipsychotics, we should cautiously investigate any features of NMS and should not exclude a diagnosis of NMS too early in cases where high body temperature is not primarily evident. Thus, it is suggested that attention for any sign or symptom of NMS should be well thought-out in patients receiving long acting APs concurrently with ECT.

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