Clozapine-Associated Neuroleptic Malignant Syndrome Followed by Catatonia: A Case Report

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Objective: Neuroleptic malignant syndrome (NMS) is a rare life-threatening condition associated with the use of antipsychotics and other drugs that influence dopaminergic transmission. Although NMS is typically associated with classical antipsychotics, it can also be induced by atypical antipsychotics. In this paper, we report a case of NMS associated with clozapine use.

Case: A 27-year-old male was diagnosed as schizophrenia in 2006 and zuclopenthixol depot was administered parenterally. Following the second injection, NMS was diagnosed and he was switched to clozapine. After 4 years of clozapine use, one day, he suddenly stopped eating, stayed in bed all day, and had incontinence. Upon examination at our hospital the patient had muscle rigidity, high fever, leukocytosis, and a high creatine phosphokinase level, and NMS was diagnosed. He was put on bromocriptine. NMS resolved, but psychotic relapse and catatonia developed. 10 sessions of electro convulsive treatment (ECT) were administered. Quetiapine 25 mg/day was introduced and titrated up to 600 mg/day afterwards. He has been using quetiapine 600 mg/day for 18 months and at the time this manuscript was written has not had any signs of psychosis or NMS.

Conclusion: NMS is usually induced by the use of agents with high dopaminergic affinity. Incomplete or extraordinary NMS cases have been reported due to clozapine and atypical antipsychotics. The presented case is noteworthy due to the complete and typical presentation of NMS. It should always be kept in mind that all atypical antipsychotics including clozapine have the probability to induce NMS although not common.

Keywords: Clozapine, antipsychotics, neuroleptic malignant syndrome, catatonia

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a life threatening condition caused by neuroleptics and other drugs that affect dopaminergic transmission. NMS is characterized by muscle rigidity, and high body temperature. These symptoms may be accompanied by changes in the level of consciousness, mutism, tremor, diaphoresis, dysphagia, incontinence, elevated or labile blood pressure, tachycardia, leukocytosis, elevated liver enzymes, and laboratory evidence of muscle injury. Its development has been associated with a hypodopaminergic state that disrupts heat regulation (Janicak and Beedle 2009). In addition, other neurotransmitters, such as serotonin, gamma amino butyric acid, acetylcholine, and noradrenaline, have also been proposed (Duggal and Kithas 2005; Pelonero et al. 1998). Probable complications of NMS due to rhabdomyolysis include acute renal failure, venous thromboemboli, multiple system failure, and aspiration pneumonia (Bhanushali and Tuite 2004). Dehydration, hyponatremia, agitation, use of restraint, and intramuscular antipsychotic administration are among the most frequently reported risk factors associated with NMS (Berardi et al. 1998).

NMS could be seen with the use of dopamine antagonists, with the withdrawal of antiparkinsonian medications, and rarely, with abrupt discontinuation of antipsychotics. The reported incidence of NMS varies from 0.5% to 3% among patients using typical antipsychotics (Bottoni 2002), but following frequent use of atypical antipsychotics, NMS incidence has declined to 0.01%-0.02% (Stubner et al. 2004). The incidence of NMS among patients using pure atypical antipsychotics is not known yet; however, cases of NMS associated with all types of atypical antipsychotics have been reported (Patel and Brunetti 2010; Singh and Wise 2010; Srivastava et al. 2009; Abay and Kose 2007; Ozen et al. 2007;

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Duggal 2007; Bourgeois et al. 2002; Baciewicz et al. 2002; Dave 1995). Nevertheless, in their review of the literature from 1966 to 1997, Pelonero et al. (1998) concluded that all antipsychotics, including new atypical ones, are capable of inducing NMS.

Caroff et al. (2000) claimed that atypical antipsychotic induced NMS cases generally met the criteria for NMS, although some could also manifest as incomplete NMS cases lacking some symptoms such as muscle rigidity. Caroff et al. (2000) added that body temperature above 38 °C was significantly less common in NMS cases associated with atypical antipsychotic use. In a review on NMS and atypical antipsychotics, Trollor et al. (2009) concluded that although atypical antipsychotic-induced NMS can present in mild and atypical forms, it usually manifests in classical forms. On the other hand, compared with other atypical antipsychotic-induced NMS cases, clozapine-associated NMS cases could be seen in different clinical manifestations and special consideration is needed for accurate diagnosis (Trollor et al. 2009; Caroff et al. 2000).

This paper reports a case of clozapine-associated NMS and reviews and discusses the literature on NMS and clozapine use.

CASE

A 27-year-old single, male university graduate began to have symptoms in 2006 while attending university, which included social isolation, lack of communication with others, food refusal, and spending entire days alone in his room. He was taken to a psychiatrist and was administered intramuscular zuclopenthixol depot, as he refused to take oral medication. Following the second injection (2-3 weeks after the first), his general medical condition declined, and he experienced unconsciousness and rigidity. He was taken to a hospital, diagnosed as NMS, and treated for 56 days in the intensive care unit.

Following resolution of NMS, he presented to a university hospital and was diagnosed as schizophrenia at the outpatient psychiatry clinic. At that time the patient was socially isolated, had auditory hallucinations that swore at him or said his name, and had delusions of persecution that made him suspect he was being followed and could be killed. He would also spend entire days sitting in bed not doing anything else. After an unsuccessful olanzapine trial, he was switched to clozapine. All symptoms resolved with clozapine 200 mg daily. For the next 4 years he used clozapine 200 mg daily and was in full remission. Then, the clozapine dose was reduced to 150mg daily and 15 days after this dose reduction he again began staying in bed all day, refused to eat, and had hypersomnia.

When his relatives noticed that he had incontinence, they took him to a hospital. On his admission to the hospital, his body temperature was 39-40 °C, leukocyte count was 16,000, creatinine kinase level was 2000 U/L and he had rigidity. He was again diagnosed as NMS. He was hospitalized in the neurology intensive care unit, and was given supportive treatment and bromocriptine; clozapine was discontinued. On the fifth day of admission he was discharged because his general clinical condition had improved and he had psychomotor agitation. He was then taken to our hospital by his relatives. He was evaluated by psychiatrists and neurologists, and was hospitalized in the neurology intensive care unit. During his stay in the clinic of neurology, he had a fever above 39 °C, leukocytosis of 11,000, creatinine kinase level of 100,000 U/L, tachycardia (120 bpm), labile blood pressure, severe muscle rigidity, and diaphoresis. Bromocriptine 15 mg daily, along with symptomatic and supportive treatment were administered. In one week time, his general health improved, his fever, leukocytosis, and high creatinine kinase level dropped, and bromocriptine was withdrawn. The patient underwent a psychiatric consultation and was given diazepam 15 mg daily and transferred to the psychiatry inpatient unit.

Upon admission to the psychiatry ward he had clear consciousness, flat affect, frequent derailments, clang associations, and echolalia. He sometimes had mutism during the day that lasted for many hours, during which time he also had negativism, immobility, and waxy flexibility. Sometimes he had psychomotor excitation. He refused to eat. Creatinine kinase was 223 U/L, leukocyte count was 7620. Routine laboratory investigations were within normal limits. He was diagnosed as schizophrenia and catatonia. He was evaluated weekly using the positive and negative syndrome scale (PANSS) (Kostakoğlu et al. 1999; Kay et al. 1987). PANSS total score was 168 at admission.

In consideration of the fact the patient had NMS and catatonia, electro convulsive therapy (ECT) was scheduled. Diazepam was gradually withdrawn. After the necessary investigations were completed, bilateral ECT with anesthesia every other day was started. After the first ECT session his negativism improved significantly and he began to eat and communicate. During the interviews he talked about his auditory hallucinations, and delusions of reference, persecution, thought withdrawal, and thought broadcasting. After 10 sessions of ECT, signs of catatonia, delusions, and hallucinations disappeared. PANSS total score was then 45. He was put on quetiapine 25 mg daily and increases of 25 mg daily were planned to achieve an effective dose. One week later, when the daily dose of quetiapine was 100 mg, the patient again had auditory hallucinations and delusions of reference. Three sessions of maintenance ECT was administered weekly and the quetiapine dose was increased as planned. When the quetiapine dose was 450 mg daily, ECT was stopped. Delusions of reference disappeared, but auditory hallucinations persisted. Then, quetiapine was increased to 600 mg daily and all

negative and positive symptoms disappeared gradually. The patient was discharged.

At the time this manuscript was written the patient was being followed-up at the outpatient unit, was taking quetiapine 600 mg daily and had been in full remission for 18 months. He did not have any positive or negative symptoms (PANSS total score = 30), signs or symptoms of NMS, nor extrapyramidal side effects. He has been holding a job for the last one year.

DISCUSSION

Clozapine is an atypical antipsychotic with a broad range of receptor affinity and multiple receptor antagonistic activity. It has a relatively high 5HT2A/D2 receptor affinity ratio. It has also affinity for D1, D3, D4, and D5 receptors. It has low affinity for dopamine D2 receptors, whereas its affinity for D4 receptors is especially high. Its affinity for serotonin 5HT2A and 5HT6 receptors is similar and high. In addition, clozapine acts as a partial agonist on 5HT2C, 5HT7, 5HT3, and 5HT1A receptors. It has particularly high affinity for α1, M1, and H1 receptors, and acts on α2, M5, M4, M3, M2, and H3 receptors as well (Yağcıoğlu and Gürel 2010). The low incidence of extrapyramidal side effects associated with clozapine might be due to its relatively high D1 versus D2 and 5HT2 versus D2 receptor affinity, and its low D2 receptor occupancy (Iqbal et al. 2003).

The risk of NMS, as the frequency of extrapyramidal side effects, appears to be correlated with the dopamine receptor binding affinity of drugs. In contrast, the lower D2 receptor occupancy of clozapine, as compared to all other atypical and typical antipsychotics, does not prevent it from causing NMS (Velamoor 2001). Therefore, the pathophysiology of NMS is suggested to be complex, involving a cascade of dysregulation in multiple neurochemical and neuroendocrine systems (Strawn et al. 2007). Clozapine rarely causes NMS. The first case of clozapine-associated NMS was reported in 1986 (Pope et al. 1986). In their review Ananth et al. (2004) identified 21 cases of clozapine-associated NMS that met DSM-IV diagnostic criteria. Patients with clozapine-associated NMS differ from those with NMS due to other atypical antipsychotic drugs in that they are less likely to experience extrapyramidal side effects, such as tremor and rigidity (Trollor et al. 2009; Caroff et al. 2000). Sanchdev et al. (1995) claimed that patients with clozapine-induced NMS cases had fewer motor symptoms and slightly elevated creatinine kinase. Moreover, delayed elevation of creatinine kinase was also reported (Gambassi et al. 2006). On the other hand, tachycardia, diaphoresis, and mental status changes were reported more frequently in patients with clozapine-associated NMS (Karagianis et al. 1999).

The presented case had marked tachycardia and diaphoresis, as in other reported cases of clozapine-associated NMS; however, the presented case's classical and complete NMS presentation with severe muscle rigidity and elevated creatinine kinase set him apart from most of other clozapine-induced cases. Furthermore, the presented patient did not have any of the risk factors associated with NMS. Psychomotor agitation, dehydration, use of restraint, mental retardation, and affective disorders are among the risk factors for NMS (Viejo et al. 2003; Susman 2001). Antipsychotic-associated risk factors are high dosage, rapid dose escalation, recent commencement of antipsychotics, and intramuscular or depot antipsychotic administration (Viejo et al. 2003). However, the presented case had been using low dose clozapine for 4 years and did not have any additional risk factors. On the other hand, existing abnormalities in dopaminergic activity and dopamine receptor functions of the central nervous system have been suggested to be associated with the risk of NMS (Strawn et al. 2007), as well as the role of individual factors and genetics (Pelonero et al. 1998). Despite the vast number of patients using antipsychotics, very few patients develop NMS, which is indicative of the importance of individual factors and leads us to think that the presented patient may have had an individual predisposition for NMS, in addition to his being previously diagnosed as NMS.

Another important point is that our patient developed NMS after a reduction in the clozapine dose. Discontinuation or a reduction in the dose of clozapine may cause cholinergic system hyperactivity that results in diaphoresis, tremor, rigidity, agitation, and fever, which may be confused with the symptoms of NMS (Margetic and Margetic 2005). Additionally, it is well known that symptoms of clozapine withdrawal emerge frequently during the first few days of its withdrawal (Ahmed et al. 1998). The presented patient did not have any symptoms for the first 15 days after the dose of clozapine was reduced; therefore, clozapine withdrawal syndrome was excluded. Serotonin syndrome, which has a similar clinical presentation as NMS and can be associated with atypical antipsychotic use (Sternbach 2003), was also excluded, as the patient did not have myoclonus, hyperreflexia, or gastrointestinal symptoms, and had not used any additional serotoninergic agents.

The presented case developed catatonia following NMS. Cases of clozapine withdrawal catatonia have been reported (Hung et al. 2006; Yeh et al. 2004; Lee and Robertson 1997). In fact, clozapine use has been recommended for recurrent catatonia cases (Hung et al. 2006). In the presented case, the development of catatonia was most likely associated with the abrupt discontinuation of clozapine because of NMS. Yet, some authors interpret NMS and catatonia within the same spectrum (Fink 1996; White 1992). On the other hand, Lee (2007) suggested that NMS had catatonic and non-catatonic variants, as he observed catatonia in 64% of NMS cases he

investigated. As such, there is the possibility that the catatonic features in the presented patient could have been a part of the NMS. It is also known that catatonia increases the risk of NMS and that patients with catatonia require special consideration (Janicak and Beedle 2009).

When NMS is accompanied by catatonia, a rapid and effective treatment that will involve both conditions is required. ECT is known to be an effective treatment in such cases (Choi et al. 2011). ECT was the treatment of choice in the presented case and the outcome was successful. Long-term treatment is another important issue in patients that recover from NMS. The unpredictable emergence and course of NMS, along with the risk of recurrence, complicates long-term treatment planning (Susman 2001). We preferred quetiapine, an atypical antipsychotic with a high 5HT2/D2 receptor affinity ratio. As recommended for patients with a recent history of NMS, we chose to administer an antipsychotic different than the one that induced NMS. As recommended, we started with a very low dose and the effective dose was achieved via very slow dose titration (Janicak and Beedle 2009). We achieved full remission and the patient had not had any signs or symptoms of NMS at the time this manuscript was prepared. As recommended in the literature, the patient is being followed-up closely.

In conclusion, NMS is a life-threatening condition. Any antipsychotic can induce NMS at any time (Harrison and McErlane 2008). Early diagnosis is the most effective step in preventing NMS from following a severe and fatal course (Fekadu and Bisson 2005). NMS can present with various atypical manifestations and diagnosis is possible only in response to a high level of suspicion. The presence of only 1 NMS symptom should be sufficient for clinicians to consider NMS in the differential diagnosis of patients using antipsychotics.

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