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A Severe Neuroleptic Malignant Syndrome Treated with Daily Electroconvulsive Therapy: A Case Report

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SUMMARY

Neuroleptic malignant syndrome (NMS) is a rare but life-threatening condition caused by dopamine modulating medications, particularly antipsychotics. First-line treatments of neuroleptic malignant syndrome are supportive care, discontinuation of the offending agent and pharmacotherapy. In drug-resistant and severe situations, electroconvulsive therapy (ECT) is recommended as well. In this paper we present a 23-year old male with bipolar disorder who was treated with multiple injections of zuclopenthixol long acting and depot forms for a recent manic episode and developed NMS. The patient was transferred to an intensive care unit, medical management was initiated including benzodiazepines, bromocriptine and dantrolene. Due to the inadequate response after several days, ECT (bitemporal electrode placement, brief-pulse, on a daily basis) was initiated. After 17 sessions, NMS relieved and there was no need for maintenance ECT. The patient is under follow-up care for 3 years with no cognitive and physical sequela.

Keywords: Electroconvulsive therapy, neuroleptic malignant syndrome, bipolar disorder

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a severe, life-threatening reaction to antipsychotics and dopamine-modulating agents. Cardinal symptoms of NMS are rigidity and fever, other symptoms include: autonomic instability, mental status changes and laboratory abnormalities, especially those showing muscle damage (leukocytosis, elevated serum creatine kinase, transaminases, lactate dehydrogenase) (Adnet et al. 2000). NMS has a high morbidity and mortality rate if left untreated (Tse et al. 2015). Treatment of NMS includes discontinuation of the offending agents, supportive therapy, treatment with benzodiazepines, dantrolene, dopamine-enhancing agents (amantadine, bromocriptine) and electroconvulsive treatment (ECT) for severe and drug resistant conditions (Tse et al. 2015, Caroff and Mann 1993). NMS with depot antipsychotics is expected to be a more severe condition than NMS with oral antipsychotic treatment.

A case of drug resistant, severe and life-threatening NMS induced by zuclopenthixol acetate and decanoate injections that resolved after intensive ECT is presented below. The patient gave free, informed consent for the publication of this case.

CASE HISTORY

23-year-old man with a history of Bipolar I Disorder who had been in remission with lithium 1500 mg/d for 6 years, presented with manic symptoms to the psychiatry outpatient clinic. On admission lithium blood level was 0.66 mmol/L. Lithium was increased to 1800 mg/d and 200 mg/d quetiapine was added to his regimen. After 3 weeks, he presented to the emergency department with agitation, dysphoria, psychotic symptoms and disorganized behavior; zuclopenthixole acetate 50 mg intramuscular was administered and lorazepam 4 mg/d was added. Starting from twenty days after the first injection, zuclopenthixol acetate 50 mg intramuscular injections were administered for 3 more times with 3-day intervals, and with the last one zuclopenthixol decanoate 200 mg intramuscular was also administered. One week after the last depot injection,

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he was found as sedated, more compliant with no psychotic symptoms but with mild cogwheel rigidity and bradykinesia on follow-up. Biperiden 2 mg/d was added to his regimen. Two weeks after the depot injection, patient was brought to the emergency department with dysarthria, dysphagia and diaphoresis. On physical examination, diaphoresis and mild rigidity was observed, body temperature was 36 ^{0}C, lithium blood level 1.17 mmol/L (normal range 0.6-1.2), creatine kinase (CK) 485 U/L (normal range <171), and myoglobin 57.6 ng/mL (normal range 17.4-105.7). After 3 mg lorazepam P.O. and intravenous hydration for 24 hours, the patient developed confusion, still with a temperature of 36 ^{0}C, a CK of 501 U/L and an increase in neutrophil count without leukocytosis (6800/ml and 10100/ml respectively). With these findings and the history of depot antipsychotic injection, the patient was diagnosed with neuroleptic malignant syndrome (NMS), transferred to intensive care unit (ICU), lithium stopped, intravenous hydration and lorazepam 8 mg/d P.O. was initiated.

On the first day of ICU stay, bromocriptine 3X2.5 mg was initiated upon increase in rigidity, tachycardia, and autonomic instability (hypertensive attacks). On the second day of ICU stay CK levels increased (344 U/L, 781 U/L,1065 U/L on the same day), myoglobin level increased to 424 ng/mL, lorazepam and bromocriptine dose was titrated to 10 mg/d and 3X5 mg/d respectively. Bilateral ankle clonus was detected, a computed tomography of brain revealed no acute intracranial pathology, and an electroencephalography (EEG) was performed with no epileptiform anomaly. His drug panel was negative. On the 6th day the patient developed a fever (38.5 ^{0}C) for the first time. Due to unresponsiveness to the medical treatment, worsening mental status, increase in CK levels and transaminases, and developing leukocytosis, a decision was made for ECT treatment on the 7th day of ICU stay.

ECT was started on a daily basis including weekend in ICU. SpECTrum 5000Q® (MECTA Corporation), bitemporal electrode placement with brief pulse settings was used for ECT sessions. The duration and quality of the seizures were followed with both cuff-method and EEG monitoring. Thiopental, rocuronium and sugammadex was preferred for anesthesia, muscle relaxation and the reversal of neuromuscular blockade, respectively. During the first 3 ECT treatments, the patient remained confused and rigid, hyperthermia, leukocytosis and autonomic instability persisted but CK levels decreased gradually. On the day of 4th ECT, CK levels started to rise again (1752 U/L, 3236 U/L and 4409 U/L respectively on the same day); bromocriptine dose increased to 3X10 mg/d and dantrolene 80 mg per 2 hours intravenous infusion added to the medical therapy. The day after 5th ECT the patient became hypoxic and has been intubated by the anesthesiology team. A postero-anterior chest X-ray and computed tomography of thorax revealed diffuse infiltration, the patient was diagnosed with pneumonia, antimicrobial therapy started; the same day ECT treatment was stopped due to hypokalemia and KCl infusion started; an MRI of brain revealed no acute pathology. After three days ECT treatments were resumed on a daily basis. Dantrolene treatment was stopped on the day of 6th ECT session. On the 8th ECT day, CK was found 4641 U/L and ECT was continued on daily basis. After the 12th ECT the patient was extubated, and ECT was skipped on that day. After the 13th ECT, autonomic instability decreased, CK levels dropped to 498 U/L on the same day and the patient started to respond to verbal stimulus. Lorazepam dose was decreased and respiratory rehabilitation was initiated. Fourteenth ECT was done 6 days after the previous one, CK level decreased to 91 U/L and the patient was transferred to the psychiatry inpatient unit. A total of 3 ECT sessions were administered once weekly at the psychiatry inpatient unit. A total of 17 ECT sessions were administered during the index course, with no maintenance ECT needed. Clonazepam 2 mg/d was started by the neurology department for involuntary movements in the extremities, and valproic acid was started for the primary psychiatric disorder. During the hospital stay, intensive physical therapy and speech therapy were done. Patient was discharged from the hospital after a total of 3 months stay. Upon discharge, he got 30/30 points from Mini Mental State Exam. The patient is still followed-up with remission without any physical or cognitive sequela.

DISCUSSION

The case of a patient was presented in this report who developed severe NMS after several intramuscular injections of a first generation depot antipsychotic and treated with daily ECT. The persistent and intensive ECT administration despite the worsening medical condition of the patient including unconsciousness and pneumonia, was a life-saving choice in this case.

The risk factors for developing NMS are still controversial but generally thought to include first generation antipsychotic use, young age, being male, concomitant lithium use, rapid dose increase, parenteral administration, and psychomotor agitation which all of them were present for our patient (Tse et al. 2015, Caroff and Mann 1993). The patient also had a few atypical features including no hyperthermia and very mild rigidity at the beginning of the NMS picture while he developed full syndrome in the following days. Despite presenting with an atypical picture, considering the history of depot antipsychotic and the presence of risk factors, NMS was diagnosed promptly, and a positive treatment response was obtained as a result of the early diagnosis, being followed up in the intensive care unit and having applied an aggressive treatment.

The differential diagnosis of NMS includes other disorders presenting with similar symptoms like extrapyramidal side effects, serotonin syndrome (SS), infections, agitated delirium, and status epilepticus (Tse et al. 2015). A differential diagnostic work-up including cranial MRI, EEG, drug panel, urine analysis and culture was done for our patient in every step. Clonus in extremities is one of the symptoms of SS which was detected in our patient on the first days of hospitalization, but with the lack of gastrointestinal symptoms, hyperreflexia, ataxia and with no history of serotoninergic agent use SS was not considered in our patient (Nisijima 2015). Malignant catatonia should also be considered in the differential diagnosis of NMS (Fink 1996), but the absence of fever at the beginning phase and the history of multiple antipsychotic injections make the diagnosis of NMS most possible in our case.

The use of ECT is recommended for the treatment of NMS especially in drug-resistant or severe cases as a life-saving option where a prompt response is needed (Trollor and Sachdev 1999). A comparison of ECT with other choices of treatment is unlikely due to the rarity of NMS, the information comes from mainly case reports and a few case series. Recently, in a review examining the NMS treatment recommendations in international guidelines, it was reported that ECT is recommended for treatment in 8 of 14 treatment guidelines; however, all of these guidelines have made their decisions based on case reports, case series, and expert opinions (Schönfeldt-Lecuona et al. 2020). The safety of ECT use in patients who already have autonomic instability may be controversial, however a thorough investigation and correction of the complicating situations (cardiovascular conditions, electrolyte disturbances, infections) would help to make the procedure uneventful most of the time. In our case, NMS in the presence of a depot antipsychotic use, failure of drug therapy and the worsening condition of the patient necessitated an urgent intervention.

Although depolarizing agents are accepted as safe to be used in ECT in NMS patients, considering a possibility of malignant hyperthermia development rocuronium, a non-depolarizing agent, was preferred in this case (Trollor and Sachdev 1999). In the literature, cases were reported which rocuronium was preferred instead of succinylcholine due to the risk of malignant hyperthermia development as well as hyperkalemia and cardiac arrhythmia (Ramamoorthy et al. 2011, Şanlı et al. 2014).

The standard frequency of ECT administration is generally two or three times a week depending on the circumstances of the clinics (Charlson et al. 2012). Increasing the treatment frequency more than the standard three times a week is a way of enhancing the efficacy of treatment and decreasing the time needed for a response. Some research reported 5 times/week ECT administration in small groups and found both faster efficacy and no compromise in cognition (Ghaziuddin et al. 2017, Rasmussen et al. 2016). None of the guidelines including treatment recommendations for NMS provide a detailed explanation on when and in what condition ECT should be initiated, nor do they suggest parameters of application such as electrode placement, frequency of application, and duration of the treatment (Schönfeldt-Lecuona et al. 2020). The frequency of ECT application is not always reported in the case reports, though some report 2-3 applications per week. Only Welsh et al. reported that they used daily ECT in one case; this one was a severe NMS case with no response to drug treatment for 9 weeks and ultimately had ECT, but ECT was discontinued after a total of 5 sessions due to the development of cardiac arrhythmia (Welsh et al. 2016). Considering the lower risk of cognitive deterioration based on the young age of the patient paired with the emergency of the situation, ECT administration on a daily basis was preferred in our case. Although it is seen that unilateral ECT is more preferred in the treatment of NMS in some studies (Trollor et al. 1999), bitemporal ECT is recommended as the first choice for patients with severe and emergency situations in ECT guidelines (Welsh et al. 2016). In our patient, bilateral application was preferred due to the severe NMS.

The patient has been stable for more than 3 years at the time of this report.

In conclusion, NMS is a medical emergency which may also present with an atypical picture after exposure to antipsychotic therapy. Fast recognition and intensive treatment are life-saving in this condition. While discontinuation of the offending agent and supportive therapy are sufficient in mild cases, more rigorous effort including use of dopaminergic agents and/or ECT is needed for more severe cases. In severe cases, accompanying autonomic instability, infections or impaired consciousness may cause hesitation about the use of ECT, but intensive treatment with daily ECT in these cases can be life-saving upon necessary precautions taken.

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