

## INTENSIVE ELECTROCONVULSIVE THERAPY IN DRUG RESISTANT NEUROLEPTIC MALIGNANT SYNDROME - CASE REPORT

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### INTRODUCTION

Neuroleptic malignant syndrome (NMS; ICD-10 code: G21.0) is a rare, although potentially life-threatening adverse reaction to antipsychotic drugs and other dopamine-modulating agents. Symptoms of NMS include: severe muscle rigidity, fever, autonomic instability, mental status changes and laboratory abnormalities (elevated serum levels of creatinine kinase, aldolase, transaminases, lactic acid dehydrogenase, decreased serum iron concentrations, metabolic acidosis and leukocytosis) (Strawn et al. 2007). Almost all antipsychotics have been associated with NMS, both typical (Caroff & Mann 1993) and atypical (Caroff et al. 2000). Central dopamine hypoactivity induced by withdrawal of dopaminergic agents or antipsychotics blocking dopamine receptors plays a crucial role in triggering NMS (Mann et al. 2000, Živković et al. 2010). Almost all cases of NMS develop within 30 days after initiation of antipsychotic treatment (Caroff & Mann 1988). Differential diagnosis should include neuroinfections, agitated delirium, malignant catatonia, status epilepticus, extrapyramidal side effects, malignant hyperthermia, serotonin syndrome and others (Strawn et al. 2007). Several rating scales were developed to track the clinical course of NMS. Francis-Yacoub NMS Rating Scale is a 23-item scale evaluating motor, behavioral, autonomic and laboratory domains of NMS (Yacoub et al. 2004).

Usually NMS is self-limiting after antipsychotics are discontinued with average duration of recovery in the range of 7-10 days (Caroff & Mann 1988). Treatment of NMS includes cessation of an antipsychotic, benzodiazepines, dopaminergic agents (bromocriptine, amantadine) and dantrolene sodium (Strawn et al. 2007). Volume resuscitation, correcting electrolyte abnormalities, cooling measures and correcting risk factors are paramount. Electroconvulsive therapy (ECT) is effective in many cases of NMS, even if drug therapy has failed (Trollor & Sachdev 1999). A systemic review of literature data indicates that antipsychotic use following NMS may be re-initiated, however a likelihood of developing another NMS is up to 30% (Pope et al. 1991), even for clozapine (Manu et al. 2011).

A case of severe drug resistant severe neuroleptic malignant syndrome induced by clozapine and haloperidol that successfully resolved after intensive electroconvulsive therapy is presented below. The patient gave free, informed consent for the publication of his case.

### CASE PRESENTATION

A 44-year-old Caucasian man with a 23-year history of paranoid schizophrenia was admitted to the hospital for worsening of mental condition: psychomotor agitation, sleeplessness, and verbal aggressiveness lasting for about a month. Prior to this hospitalization he was relatively stable for approximately 18 years and had no previous history of neuroinfections, organic brain lesions or episodes of catatonia. On admission he was taking clozapine (500 mg/day) and haloperidol (10 mg/day), both were administered orally. No intramuscular antipsychotics were administered previously. No signs of malnutrition or dehydration were found. Despite increasing doses of both antipsychotics before admission, he was more psychotic, agitated, had bizarre ideas, persecutory delusions, religious delusions, delusions of control, auditory hallucinations. Verbal aggression was present. By the third day he became febrile (38.0°C) with increased muscle rigidity, muscle tremor, sialorrhea. Both antipsychotics were discontinued and diazepam 10 mg every 8 hours was administered IM (intramuscular). Laboratory studies showed WBC (white blood cells)  $24.1 \times 10^9/L$ . Serum levels of creatine phosphokinase (CPK) was elevated to 2936 U/L (norm: 24 - 190 U/L). Serum level of C-reactive protein (CRP) was 111.30 µg/dL (norm: 0.0 - 5.0 µg/dL). Antibiotic therapy was initiated (cefuroxime  $3 \times 1.5$  g, metronidazole  $3 \times 0.5$  g) together with 20% mannitol  $3 \times 100$  ml IV. He was referred to the unit of infectious diseases for a consultation with suspected neuroinfection. Brain CT imaging revealed no abnormalities. Slightly lowered glucose level in the cerebrospinal fluid (41.0 mg/dL; norm: 45.0 - 75.0 mg/dL) was found. Meningitis was excluded. Due to increasing CPK levels (7192 U/L on the same day, 5729 U/L on the next day) the patient was transferred to the

intensive care unit (ICU) with the diagnosis of neuroleptic malignant syndrome. Because of acute respiratory failure he was intubated and mechanically ventilated for 25 days. Treatment included: amantadine 1 × 500 ml IV (intravenous); lorazepam 10 mg/day; bromocriptine 15 mg/day; diazepam 10 mg IV (when needed). Mannitol, furosemide, fraxiparine, metoprolol were also administered. Brain magnetic resonance imaging revealed single foci up to 3 mm in diameter described as either ischemic, demyelination or post-inflammatory lesions. Serum CPK levels on admission to the ICU were 8241 U/L, on discharge - 37 U/L. After 50 days of ICU treatment the patient was transferred to our unit for further psychiatric treatment.

On admission his mental condition was severe: he was conscious but there was no logical contact with him, he was agitated, very disorganized and mutistic. Serum CPK levels were 186 U/L. Severe autonomic symptoms were observed: tachycardia (up to 140 beats/minute) and intense diaphoresis. Increased muscle rigidity was present in all extremities. Physical examination revealed also multiple contractures involving the lower and upper extremities. He had a nasogastric tube and a urinary catheter placed. Francis-Yacoub NMS rating scale was used to evaluate clinical improvement (see Table 1): initial result was 53, on Day 52 the score was 4 and 0 at discharge. Treatment initiated at the ICU

was continued: amantadine 200 ml/day IV, lorazepam 10 mg/day, bromocriptine 15 mg/day and dantrolene sodium 4 × 20 mg/day IV in addition to cooling, rehydration and subcutaneous heparin for prophylaxis of deep venous thrombosis. Due to an urgent indication for electroconvulsive therapy (ECT) and the fact that the patient was unable to give an informed consent for the therapy, a local court was informed, which gave permission for the treatment on the next day. The patient was qualified for ECT by a neurologist, internist, ophthalmologist and anesthesiologist for life-saving indications. Lorazepam and on demand diazepam were gradually discontinued by Day 14.

The first ECT procedure was done on Day 6. ECT was performed using a brief bipolar pulse from a constant-current Thymatron System IV machine (Somatics Inc, Lake Bluff, IL). A total of 19 bifrontotemporal ECT sessions (LOW 0.5 program, which delivers a 0.5 ms brief pulse that automatically adjusts the frequency to maximize stimulus train duration at each dose) were performed. Detailed data on individual sessions are shown in Table 2. Interestingly, despite using maximum (100%) charge we were unable to achieve seizures lasting more than 30 seconds, which is generally considered to be an adequate convulsive dose. Nevertheless, clinical efficacy of the therapy was very good.

**Table 1.** Francis-Yacoub NMS scores

	Day 1	Day 3	Day 6	Day 13	Day 17	Day 24	Day 29	Day 38	Day 52
Date	14.04	16.04	19.04	26.04	30.04	7.05	12.05	21.05	4.06
Score	53	47	42	40	42	15	24	13	4

**Table 2.** Parameters of bifrontotemporal ECT sessions (LOW 0.5 program)

Session	Date	Energy	Duration	Medications used for anesthesia
1	19.04	50%	14 sec	C 2 mg; P 120 mg
2	21.04	60% 75%	15 sec 10 sec	C 2 mg; P 140 mg
3	23.04	70%	21 sec	C 2 mg; E 8 mg
4	26.04	75%	32 sec	C 2 mg; P 80 mg; E 12 mg
5	28.04	75%	19 sec	C 2 mg; P 30 mg; E 12 mg
6	29.04	85%	18 sec	C 2 mg; P 60 mg; E 12 mg
7	30.04	95%	32 sec	C 2 mg; P 30 mg; E 12 mg
8	04.05	95%	28 sec	C 2 mg; P 30 mg; E 2×12 mg
9	05.05	100%	30 sec	C 2 mg; P 30 mg; E 13 mg
10	06.05	100%	25 sec	C 2 mg; P 30 mg; E 12 mg
11	07.05	100%	27 sec	C 2 mg; P 30 mg; E 13 mg
12	10.05	100%	15 sec	C 2 mg; P 30 mg; E 13 mg
13	11.05	100%	20 sec	C 2 mg; P 30 mg; E 13 mg
14	12.05	100%	20 sec	C 2 mg; E 14 mg
15	14.05	100%	8 sec	C 2 mg; P 30 mg; E 13 mg
16	17.05	100%	15 sec	C 2 mg; P 30 mg; E 13 mg
17	21.05	100%	31 sec	C 2 mg; P 50 mg; E 15 mg
18	26.05	100%	16 sec	C 2 mg; P 80 mg; E 17 mg
19	02.06	100%	16 sec	C 2 mg; A 0.5 mg; E 19 mg; P 50 mg

C = clemastine; E = etomidate; P = propofol; A = atropine

In the course of ECT physical condition of the patient was fluctuating. Increased body temperature (up to 39.1°C) was present despite regular use of antipyretics. Bacterial infections of the respiratory and urinary tract required antibiotic treatment. Fluconazole had to be administered due to oral candidiasis. Deep heel ulceration required surgical treatment. After the fourth ECT session, due to limited efficacy of first-line medications (amantadine, dantrolene sodium and bromocriptine) and because of the predominance of catatonic symptoms these medications were gradually discontinued and ECT sessions were intensified and were done on a daily basis. A gradual improvement was observed from the seventh session onward. Increased muscle rigidity was resolving gradually. Logical contact was observed periodically, although catatonic symptoms (mainly negativism and grimacing) were still recurring. Significant clinical improvement was observed after the ninth ECT session. Body temperature normalized and muscle rigidity was significantly reduced. Therefore, after fourteen sessions we were able to reduce the frequency of ECT procedures. Due to persistent psychotic symptoms, a decision to introduce clozapine was made. Clozapine was titrated very slowly from 12.5 mg/day to 400 mg/day. Gradually, the patient became less agitated and orientated to self and place. A nasogastric tube was removed and he started a full liquid diet. On Day 36 intravenous infusions of fluids were discontinued and physical rehabilitation (3 sessions per week) was started due to reduced muscle strength in all extremities. Because of anemia (hemoglobin 8.9 g/dL, red cell count  $3.17 \times 10^{12}/L$ ) and hypokalemia (3.26 mmol/L) intravenous and then oral iron and potassium supplementation was initiated. On Day 50 ECT was discontinued. Motor, autonomic and catatonic symptoms were significantly reduced. From Day 50 to 65 there was a period of labile, depressive mood, which resolved together with anemia and somatic condition. During this period cooperation with physiotherapist was very low, mainly due to pessimistic evaluation of his future and rehabilitation results. Despite increasing the dose of clozapine psychotic symptoms were recurring. These were mainly delusions of guilt and sin, delusions of reference and religious delusions. There were no episodes of aggression or auto-aggression. Suicidal ideations were absent. Clozapine was tolerated well. By Day 60 the patient started to walk without any support. On Day 114 he was discharged from the hospital in stable condition on clozapine 400 mg daily with the diagnosis of catatonic schizophrenia and neuroleptic malignant syndrome. During a one-year follow-up no symptoms of neuroleptic malignant syndrome occurred. After a year he is still on clozapine, although due to increased religious delusions its dose was increased to 500 mg daily with relatively good effect.

## CONCLUSIONS

Our case is unusual in that the patient had severe NMS symptoms (including respiratory failure) after over 60 days following the discontinuation of previous antipsychotics and despite pharmacological treatment and intensive care, and yet survived. There are other unique aspects of this case. First of all, despite previous claims (Tsai et al. 1995), it confirms later reports that NMS may occur in patients taking clozapine, either when used in monotherapy or combined with other antipsychotics. Here NMS was triggered by the not very infrequent combination of clozapine with haloperidol. Since other potential risk factors of NMS were excluded (dehydration, malnutrition, exhaustion, infection), it is assumed that the combination of antipsychotics triggered NMS. Second, NMS usually develops after introducing antipsychotic treatment. In this case the patient was taking clozapine and haloperidol for several months without any side effects. However, dosage of both agents was increased shortly before NMS occurred, thus this may have triggered NMS. This also proves that even patients with long-term history of antipsychotic treatment are vulnerable to this complication. Therefore, although the incidence of NMS is relatively low, high mortality should emphasize the need for careful monitoring after any changes in antipsychotic treatment. Third, it is thought that symptoms of clozapine-induced NMS are somewhat different from those of typical neuroleptic-associated NMS (Sachdev et al. 1995): the most commonly reported clinical features were tachycardia, mental status changes, and diaphoresis, while fever, rigidity, and elevated creatine kinase were less prominent. However, a cluster of typical features of NMS was observed here. The patient had a mixed complex of all core symptoms probably because of combined treatment with haloperidol and clozapine, although the dose of clozapine was relatively high, while the dose of haloperidol was moderate.

Withdrawing antipsychotic(s) and introducing symptomatic treatment are of top priority in case of suspected NMS. Benzodiazepines (usually lorazepam) are the first-line drugs in mild NMS. For moderate to severe NMS dopaminergic agents, dantrolene should be considered. Treatment algorithm for NMS was proposed by Strawn et al. (2007). ECT is considered as the second-line interventions. Trollor & Sachdev (1999) presented a case series of 9 patients in whom considerable improvements were shown after a course of ECT. Their literature review indicates that response to treatment is usually apparent after a few sessions. This case confirms such observation - significant improvement of general symptoms and mental condition was first observed after the seventh treatment. However, to achieve this improvement, the patient required unusually high frequency and dose of ECT procedures since less intensive ECT course turned out to be

ineffective. Subjects described by Trollor & Sachdev (1999) achieved significant improvement after 3 to 5 ECTs, while the average total number of ECTs was about 10. Harland et al. (1990) described a patient with severe and refractory NMS, which resolved after 8 ECT treatments administered over 6 weeks. For some reason the patient described here was a lot more refractory. Apart from minor MRI abnormalities, there were no other obvious factors that would be associated with such non-response to treatment. This clearly shows that it is worth to continue and intensify ECT even if initial response is inadequate, particularly if there are no other options available. We were also unable to generate seizures lasting more than 30 seconds, even if maximum charge was used and despite withdrawing benzodiazepines. This may result, at least partially, from previous long-term treatment with large doses of benzodiazepines. Interestingly, although seizures lasting less than 30 seconds are generally considered to be inadequate, it did not alter clinical efficacy of the treatment. This case also reaffirms that the response to ECT is faster than to drugs. Moreover, it is thought that ECT can reduce the risk of subsequent NMS after re-introducing antipsychotic. In this case we were able to safely restart the treatment with clozapine, a drug that previously could lead to NMS. However, it should be kept in mind that rechallenge with antipsychotic can trigger NMS in 30% of cases (Manu et al. 2011).

This case report suggests that intensive ECT may be an effective treatment for severe NMS, even if previous pharmacological treatment with several drugs of choice has failed. Because of fast onset it should be a first-line treatment in cases of severe NMS, when a prompt response is required (as in this case). We have successfully made 19 ECT sessions with excellent clinical results. Initial benefit was noted after the seventh session, while significant clinical improvement occurred after the ninth procedure. Despite poor general condition of the patient (anemia, hypokalemia, bacterial infections) ECT was safe and no complications were observed. No significant cardiovascular complications were observed. Although NMS patients may be at risk for developing malignant hyperthermia during anesthesia for ECT (Caroff et al. 1987), we observed no signs of this risk. Nevertheless, the duration of recovery was very long (over 160 days) and despite complex treatment, physiotherapy and nursing care, some permanent complications (hypoesthesia and paresis of the left hand fingers) did not resolve.

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**Conflict of interest :** None to declare.

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