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THE USE OF ELECTROCONVULSIVE THERAPY AND GENERAL ANAESTHESIA IN CATATONIC SCHIZOPHRENIA COMPLICATED BY CLOZAPINE - INDUCED PANCYTOPENIA – CASE REPORT

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INTRODUCTION

Catatonic schizophrenia is characterized with at least two of the following: catalepsy or stupor, excessive motor activity; extreme negativism or mutism; peculiarities of voluntary movement as evidenced by posturing, stereotyped movements, prominent mannerisms, or prominent grimacing; echolalia or echopraxia (American Psychiatric Association 1994). Electroconvulsive therapy (ECT) is widely used and shown to be effective and safe in patients with catatonic schizophrenia (American Psychiatric Association 2001). However, to our knowledge no case of ECT in catatonic schizophrenia **c**omplicated with pancytopenia due to clozapine sensitisation has been reported. Pancytopenia is defined as an disorder in which all three major formed elements of blood (red blood cells, white blood cells and platelets) are decreased in number (Istiaq et al. 2004).

CASE REPORT

We present the case of a 57-year-old man who was diagnosed with schizophrenia at the age of 24. Early in the course of illness he was hospitalized on several occasions and put on clozapine (dose ranging from 300-600 mg/day), thus achieving a rather stable remission. However, after the death of patient's brother in 2009, his condition significantly worsened and was admitted to a psychiatric facility. The pharmacotherapy was modified - fluphenazine and promazine were added to clozapine - but the patient was continuously psychotic and aggressive. During that period he was diagnosed with leukopenia (leukocyte count $2.3x10^9$/L) and clozapine was discontinued from the therapy. In 2010, clozapine was reintroduced in the treatment with no records of blood tests in that period. In August of 2011, the patient was referred to our Clinic as a treatment-resistant case. At admission he was very thin, extremely pale and dehydrated. Mental examination showed complete disorientation (he thought he was 200 years old and living in Pjong Jang), paranoid delusions as well as visual and auditory hallucinations. The patient's behaviour was unpredictable, varying from semistuporous to catatonic excitement when he would smash hospital doors and beds. The cognitive functions were deteriorated by a long lasting psychotic process. In the first two weeks of hospitalisation the patient attempted to escape from the department on several occasions.

The baseline tests such as serum electrolytes, routine urine examination, liver enzymes test, thyroid hormones, electroencephalogram, brain MSCT, abdominal ultrasound and hemoccult were all normal. The posterior-anterior chest x-ray showed sharply restricted nodose lesion in the posterior segment of the right lobule which was considered not significant (probably related to tuberculosis in the past) and the patient was scheduled for the regular follow up. The blood tests revealed again that the patient has developed pancytopenia (haemoglobin 93 g/L, granulocytes $1.28x10^9$/L, leukocytes $2.1x10^9$/L and trombocytes $98x10^9$/L), clozapine was removed from the therapy. The patient was examined by a haematologist – both sternal punction and spleen ultrasound showed no abnormalities. The patient was a non-smoker.

The ECT was applied with consent of the ECT team and the patient's guardian. The ECT team included a psychiatrist, an anesthesiologist, an internist, a psychiatric nurse and an anesthesiology nurse (Kuzman et al. 2012). The standard protocol was applied in this case. To avoid a possible unfavourable parasympathetic reflex after the ECT, atropine (0,01mg/kg) was given as premedication five minutes before the treatment. Following preoxigenation (100% O2) general anesthesia was induced with propofol (1mg/kg). After the loss of consciousness and eyelash reflex, intravenous succinylcholine (0.5 mg/kg) was administered for muscle relaxation and ventilation was assisted with a face mask and 100% oxygen. When fasciculation subsided and adequate neuromuscular relaxation was obtained, ECT was administered using the Thymatron Modell DG, Somatics Inc, 1995 device. Electrodes were placed bilaterally, frontotemporally, followed by the application of 800 mA, 90 Hz, short pulse wave of 1 ms, with the duration of the stimulus for 3.36 s - 3.92 s. The energy delivered to the patient was 35% - 40%, or (151.2 mC/ 34.79 J - 174.4 mC/ 39.76 J). The treatment produced a 25-28 seconds modified generalized seizure. No adverse effects occurred throughout the procedures.

The ECT was applied three times per week and he received 15 applications in total.

This led to a dramatic clinical improvement - the patient became more cooperative, started to speak with the staff and other patients, regularly joined them for lunch and spent time in the living room watching news. His delusions were present to a lesser extent and interestingly, at one point he explained that he believed we were in prison in Pjong Jang because of window security bars. Seven weeks after clozapine was removed from the therapy, all blood tests improved - haemoglobin 122 g/L, granulocytes $2.17x10^9$/L, leukocytes $3.1x10^9$/L and trombocytes $98x10^9$/L. The pharmacotherapy was continued with fluphenazine 5 mg per day, biperiden 2 mg per day and levomepromazine 100 mg per day. A year after the hospitalization patient's condition (including blood tests) was still rather stable.

DISCUSSION

We presented a patient with severe catatonic schizophrenia complicated with poor somatic condition and pancytopenia secondary to clozapine. The analysis of treatment options included several clinically relevant questions - What is the mechanism of the observed immune system sensitization? Would it be safe to introduce another antipsychotic drug? Should we wait for pancytopenia to fully recover before exposing the patient to the ECT (although the American Psychiatric Association guidelines list no absolute contraindications for the ECT)? Could general anaesthesia worsen the patient's condition as it has been reported that propofol used in anesthesia can cause bleeding due to decreased aggregation of trombocytes (Mahendran 2002)?

The literature offers limited answers to these questions. An international multi-center study estimated that drugs caused 62% of all idiopathic severe neutropenia cases in a general population (Kaufman et al. 1996). Traditionally, mechanisms for idiosyncratic drug-induced agranulocytosis have been classified as "toxic" or immune. The mechanism by which clozapine exerts a toxic effect on the bone marrow and on circulating neutrophils has been studied extensively. A drug-induced neutropenia/agranulocytosis in general, it is thought to have a large idiosyncratic (genetic) component (Flanagan & Dunk 2008). However, reports of the sudden development of clozapine-induced agranulocytosis after several years of exposure to the drug with no detectable adverse haematological effects (Patel et al. 2005) do suggest that extra-genetic factors could play a part in such patients. There appears to be no difference in the plasma clozapine concentrations in patients who either do, or do not develop agranulocytosis (Hasegawa et al. 1994). Clozapine can be oxidized to a reactive nitrenium ion, which is stable and preferably reacts with sulfhydryl groups, such as glutathione (Flanagan & Dunk 2008). The ions are normally detoxified by reduced glutathione (Flanagan & Dunk 2008). However, the ions may also either bind to neutrophils to cause cell death, or could cause oxidative stress-induced neutrophil apoptosis (Husain et al. 2006). Antineutrophil antibodies, possibly generated by reaction of nitrenium ions with neutrophil proteins resulting in hapten formation, may also be involved in the aetiology of clozapine-induced neutropenia (Flanagan & Dunk 2008). There is likely to be an immune component since the reaction occurs more quickly and is more severe on rechallenge in patients who have developed clozapine induced neutropenia (Dunk et al. 2006). A total of 38% of patients experience further blood dyscrasia on clozapine rechallenge - in 85% the second blood dyscrasia is even more severe, and in 60% longer lasting (Dunk et al. 2006). The blood dyscrasias recovery usually occurs up to four weeks after clozapine withdrawal (Panteleeva et al. 1987), but there are exceptions - in one case report thrombocytopenia and leucopenia both occurred during clozapine treatment, and persisted for almost 13 weeks (Lambertenghi Deliliers 2000).

Since positive symptoms of psychosis and motor symptoms of catatonia are most likely to decrease with the ECT (Christison et al. 1991), that was the major reason for the use of the ECT in this patient. Furthermore, other antipsychotics are potentially haematologically toxic (Tolosa-Vilella et al. 2002, Benedetti 1999), so we were afraid that introduction of another antipsychotic would further compromise patient's haematological status.

We showed that ECT (and general anaesthesia with propofol) did not worsen patient's haematological status. In fact, this was the only therapeutic tool that led to remission of illness. Our interdisciplinary medical team decided that pancytopenia was rather mild and stable and that we should not wait for full recovery of the patient's haematological status. However, the question remains how will the observed sensitization behave in future. Our patient is possibly at the risk of drug- induced pancytopenia, so all potentially hematologically toxic drugs should be given with caution, if not avoided completely; and regular haematological monitoring is mandatory.

CONCLUSION

In the case of a patient with catatonic schizophrenia complicated by clozapine - induced pancytopenia, the use of ECT and anaesthetics was safe and efficient. Although both anaesthetics and antipsychotic have potential to compromise patient's haematological status, this combination should be favoured due to faster onset of action and in treatment resistant cases. We would also like to point out that before applying ECT patients with observed clozapine sensitization to pancytopenia should be assessed by an interdisciplinary team to ensure the safest management.

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