PSYCHOLOGICAL MEDICINE

Maintenance Electroconvulsive Therapy Augmentation on Clozapine-Resistant Psychosis with Neurosyphilis

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ABSTRACT

Introduction: **Patients with neurosyphilis may present with severe neuropsychiatric sequelae which do not respond adequately even to clozapine which is regarded as the most efficacious medication for the treatment of schizophrenia. Clozapine augmentation with electroconvulsive therapy (ECT) has been shown to be an effective and safe treatment strategy for treatment-resistant schizophrenia.**

Objective: **This case report aimed to describe a patient with neurosyphilis, whose psychotic symptoms did not improve significantly although he had multiple adequate medication trials including daily doses of fluoxetine 40 mg, olanzapine 15 mg, haloperidol 15 mg, sulpiride 1,000 mg, quetiapine 800 mg, and finally clozapine 150 mg.**

Result: **The patient was stabilized with a combination of clozapine and maintenance ECT. A total of no less than 120 sessions of ECT (stimulus dose ranged 15-200% and seizure duration 8-57 seconds) were given by August 2017 while the clozapine was maintained at 75 mg bd. The patient had one episode of spontaneous seizure during induction of general anesthesia with etomidate. Otherwise, there was no documented serious adverse effect.**

Conclusion: **Maintenance electroconvulsive therapy augmentation on clozapine-resistant psychosis with neurosyphilis is effective and safe but has never been reported in the literature to the authors' knowledge. It is hoped that this case report would contribute to the scarce literature on this augmentation strategy.**

KEY WORDS

Neurosyphilis, electroconvulsive therapy, psychosis, clozapine, neuropsychiatry

INTRODUCTION

The malarial pyrotherapy for general paresis of the insane was a groundbreaking discovery in the treatment of what is now more commonly referred to as neurosyphilis[1)]. Pyrotherapy soon fell out of favor with the discovery of penicillin for the treatment of syphilis, which coincided with the advent of convulsive therapy for psychotic disorders. In 1943, a study described the use of "electric shock" ranging 2-7 times in 5 patients who had completed malaria therapy. The therapeutic value was inconclusive as all patients had persistent psychotic symptoms and developed serious adverse effects associated with the treatment[2)]. Solomon *et al* in 1948 reported 5 cases and discussed the benefits and limitations of electric shock in the psychoses of general paresis[3)]. Vilanova *et al* reported improvement of pain, incontinence, and ataxia in a patient who developed tabes dorsalis with severe neurological symptoms, despite 5 years of treatment for syphilis with arsenic, bismuth, mercury, and penicillin[4)].

Subsequent reports clearly demonstrated the therapeutic value of electroconvulsive therapy (ECT) in neurosyphlis, despite the initial setbacks due to severe adverse effects. The ECT demonstrated a calming effect for uncontrollable mania in 6 patients with general paresis of the insane[5)]. Another case report described a 67-year-old man with neurosyphilis who developed signs of depression and psychotic symptoms after he was treated with penicillin. The ECT substantially improved the psychotic symptoms with long-term positive effects, after inadequate response to haloperidol titrated up to 50 mg/day[6)]. In a recent case report, a 40-year-old man newly diagnosed with neurosyphilis during hospitalization for a psychotic state with depression responded to 8 sessions of ECT that rapidly relieved the psychotic symptoms after failure to respond to several type of antipsychotics[7)].

Nevertheless in this era of widely available penicillin and effective psychopharmacological agents, there exist subgroups of patients with neurosyphilis who fail to adequately respond to treatment. Allen *et al* reported a patient whose symptoms did not improve significantly although he had multiple adequate medication trials including daily dose of haloperidol 5 mg, citalopram 20 mg, donepezil 5 mg, oxcarbazepine 450 mg, olanzapine 20 mg, memantine 10 mg, carbamazepine 400 mg, and finally clozapine 200 mg[8)].

A strategy that can be useful in treating poor prognosis neurosyphilis is augmentation of clozapine with ECT. It has been used in clozapine-resistant schizophrenia[9-12)], albeit concerns about the side-effects like prolonged seizures and tachycardia. Despite increased risk of clozapine-related side-effects[13,14)], limited evidence from a randomized controlled trial and open-label trials suggest that ECT is an effective intervention in clozapine-refractory schizophrenia[15)]. A systematic review and meta-analysis of retrospective chart reviews, case series and case reports involving 192 patients treated with clozapine and ECT indicated and overall response of 66% and adverse effects in 14% of them[16)].

There were few case reports on neurosyphilis with psychosis in Malaysia.[17-19)] However, only the short-term treatment with antibiotics and antipsychotics was described, and none of them were treated with either ECT or clozapine. Similarly, the authors could not find in the literature any previous report on the combined use of ECT and clozapine

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for the treatment of neurosyphilis. Thus, the aim of this case report is to illustrate the ECT augmentation on clozapine-resistant psychosis due to neurosyphilis.

CASE REPORT

A 54-year-old divorced, unemployed gentleman with history of promiscuity in his youth first presented to us seven years ago with auditory hallucinations, persecutory delusions, disorganized behavior and neurological symptoms including unstable gait, myoclonic jerk, and intentional tremors. The TPHA was positive with VDRL titer of 1:16. Brain MRI showed left temporal gliosis. He was diagnosed as schizophrenia-like psychosis secondary to neurosyphilis. He was treated with intramuscular benzylpenicillin 2.4 mega unit weekly for 3 weeks, and the VDRL titer was reduced to 1:8. In February 2017, he was treated with intravenous penicillin 4 mega unit 4 hourly for 2 weeks as patient developed reactivation of neurosyphilis evidenced by the raised VDRL titer to 1:16.

The patient was treated with psychotropic agents such as fluoxetine, olanzapine and haloperidol up to daily dose of 40 mg, 15 mg and 15 mg, respectively. He developed tremors, oversedation on olanzapine and serious adverse effect, neuroleptic malignant syndrome (NMS) while on haloperidol. Afterward, he was tried on paliperidone (highest dose 150 mg monthly), sulpiride (highest dose 1,000 mg daily) and quetiapine (highest dose 800 mg daily), but showed poor to no response despite adequate dosage and duration of treatment. The case was regarded as a treatment-resistant psychosis due to neurosyphilis and clozapine was started. The patient was able to tolerate only up to 150 mg of clozapine daily as he developed constipation on higher dose.

A year after the initial presentation, ECT as augmentation strategy was initiated while clozapine was continued at 75 mg bd. The ECT was extended to maintenance treatment fortnightly and later the interval was shortened to every 10 days as he developed psychosis before the next maintenance ECT sessions. As of August 2017, the patient had undergone not less than 120 sessions of ECT. The stimulus dosage ranged 15-200% and the seizure duration 8-57 seconds. Thymatron® System IV which is capable of delivering electrical stimulus 504 mC at 100% was used. The patient had one episode of seizures that occurred during induction of general anesthesia with etomidate. Otherwise, there was no other serious adverse effect documented. Although patient still had occasional episodes of relapse due to non-compliance to ECT, but generally, he was maintaining relatively well and manageable with the combination of clozapine and maintenance ECT.

DISCUSSION

This case illustrates the difficulties in treating the psychiatric sequelae of neurosyphilis. Due to irreversible neuronal loss, success of treatment depends on early diagnosis. Failure to diagnose neurosyphilis was associated with prolonged psychosis that has been refractory to antipsychotic treatment[20]. In this case, irreversible parenchymal neurons damage and ongoing infectious process were indicated by left temporal gliosis and reactivation of infection in 2017, respectively. This is similar to a case report, in which the refractory psychiatric symptoms were thought to stem from an ongoing infectious process despite appropriate antibiotics treatment, or irreversible brain damage evidenced by cerebral atrophy, despite resolution of the central nervous system infection[8]. Another potential insult to the brain was the NMS as brain atrophy was reported following a refractory and complicated NMS[21].

During the course of illness, the symptoms were noted to be increasingly difficult to control until the patient was initiated on clozapine trial. The ECT augmentation was initially given as acute treatment, and later was extended as maintenance treatment with interval progressively shortened from fortnightly to every 10 days. This case also illustrates the safety of the combined use of ECT and clozapine. The patient did not develop any serious adverse effects. Nevertheless, the clinician must always be alert for sign of adverse effect such as myocarditis and pericarditis which can develop in older patient treated with clozapine[22]. Antipsychotics including clozapine can induced metabolic syndrome that increase the mortality risk[23], particularly since ECT itself causes significant hemodynamic changes.

CONCLUSION

The ECT was indicated in a patient with neurosyphilis and psychosis who responded inadequately to psychopharmacological agents including clozapine. Although the infection was controlled by intensive treatment with penicillin, neurosyphilis was still associated with severe psychotic symptoms. Augmentation of clozapine with maintenance ECT is effective and safe in patient with neurosyphilis with severe psychotic symptoms. It is hoped that this case report would contribute to the scarce literature on the combine use of ECT and clozapine, which is important for the development of guidelines and recommendations for the treatment of severe psychiatric complications of neurosyphilis.

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