CASE REPORT

Venous Thromboembolism (VTE) in Patient on Clozapine Therapy

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Abstract

This article describes a case of Venous Thromboembolism (VTE), was developed in a patient with treatment-resistant schizophrenia. Patient was a 35 years-old female with treatment resistant schizophrenia who was tolerating her residual symptoms of perceptual disturbances. Despite good adherence towards treatment, she never had a complete symptom-free period. Patient also attempted suicide by trying to drown herself at a nearby beach. Considering the suicidal risk and persistency of her psychosis, patient was then initiated on Clozapine therapy. Over a period of 8 weeks, gradual dose increment resulted in an improvement of her symptoms where she was reported to have less frequency of perceptual disturbances. She was reviewed weekly for both her response and tolerability towards the Clozapine treatment. Entering the 11th week of her Clozapine therapy, Patient was admitted into the hospital for left leg tenderness in which she was later treated to be having deep vein thrombosis (DVT). Ultrasound finding revealed long segment thrombus seen from external iliac vein down to popliteal vein of her left lower limb. Patient’s medication dose was maintained at the same dose up until the 16th week of her Clozapine therapy. There were no recurrences or reports of side effects and improvement of sleep patterns were reported by her but her psychotic symptoms still persists. There are always risks and benefits while treating a patient with Clozapine. Clinician should be aware of the risk of deep vein thrombosis (DVT) among treatment resistant schizophrenia patient.

Keywords: Clozapine, Atypical Antipsychotics, Treatment Resistant Schizophrenia, Venous Thromboembolism, Deep Vein Thrombosis

Introduction

Clozapine had long been reserved as a special indication for treating schizophrenia. The complexity of its receptors selectivity and binding had been proposed to be the reason behind its efficacy. In the past few decades, despite the emergence of novel antipsychotics, they failed to prove superiority to clozapine in treating treatment-resistant schizophrenia. Tolerability-wise, clozapine therapy is proven to cause less risk of extrapyramidal side effects but they are associated with rare
side effects that are potentially fatal such as blood dyscrasias and myocarditis. Seizures have occurred in patient treated with clozapine are mainly dose related. It is managed with proper dose titration or reduction [2]. Clozapine treatment resulted in significant improvements in the patient’s symptoms but it can cause alteration over the metabolism system which can lead to dyslipidemia-mediated-pancreatic-beta-cell damage, decreased insulin secretion, and insulin resistance in some individuals, later can lead to hyperglycemia and diabetic ketoacidosis [3]. Constipation is a well-known collateral side effect of antipsychotic drugs such as Clozapine which will lead to fecal impaction, megacolon, perforation and also, in some cases, death [4]. The possible mechanism for the association between clozapine and venous thromboembolism (VTE) are multifactorial [5]. VTE usually occurs when one of three factors is present: damage to the vessel wall, static blood flow, or coagulation abnormalities. Clozapine, as well as other antipsychotics, has not been shown to cause direct damage to the vasculature in humans. However, static blood flow may be influenced by sedation and the sedentary lifestyle commonly associated with psychiatric disorders, their treatment, or both5. There is also increasing evidence that clozapine may cause a variety of different coagulation abnormalities such as an increased platelet adhesion as well as aggregation [5]. It has become a common clinical dilemma to risk potentially fatal side effects against a highly efficacious treatment option.

Case Report

Miss CJ, is a 35 years old who was treated for schizophrenia since many years ago. For the past few years, she had been tolerating her residual symptoms of perceptual disturbances. Despite good adherence towards treatment, she never had a completely symptom-free period.

In late Nov 2016, Miss CJ attempted suicide by trying to drown herself at a nearby beach. It was later identified that she was reacting to the auditory and visual hallucinations that she had. Available evidence has shown that approximately 50% of patients with schizophrenia or schizoaffective disorder attempted suicide and approximately 10% of them will die of suicide . Considering the suicidal risk and persistency of her psychosis, Miss CJ was then initiated on clozapine therapy.

Over a period of 8 weeks, gradual dose increment resulted in improvement of her symptoms where she was reported to have less frequency of her perceptual disturbances. She was reviewed weekly for both her response and tolerability towards the clozapine treatment. Hyper salivation was noted into her 9th week of treatment with a clozapine dose of 225mg/day. She was then initiated on benzhexol 4mg on a daily basis.

Miss CJ continued to complain about hyper salivation and she described the condition was getting worse but she was unable to elaborate further. Further increment of benzhexol was decided by the doctor in-charge at that time to a total dose of 6mg/day in divided dosing.

By the 10th week of clozapine therapy, Miss CJ had her psychotic symptoms remitted, however, she was still complaining of similar side-effects. She persistently complained of hyper salivation. However other commonly associated side effects such as constipation, palpitation, fever and urinary incontinence were absent. Miss CJ was keen to be on the same dose of treatment as she was satisfied with her
improvement and was still able to tolerate the hyper salivation episodes. There was no evidence of any serious side effects such as agranulocytosis or any features suggesting cardiovascular complications.

Entering the 11th week of her clozapine therapy, Miss CJ was admitted into the hospital for left leg tenderness in which she was later treated to be having deep vein thrombosis (DVT). Ultrasound finding revealed long segment thrombus seen from external iliac vein down to popliteal vein of her left lower limb. Miss CJ was then initiated on warfarin by the surgical team and a dose reduction of clozapine was then decided. At the point of discharge from the hospital, Miss CJ was on clozapine 125mg/day and benzhexol 4mg/day.

Miss CJ began experiencing relapse symptoms of schizophrenia as she reported experiencing perceptual disturbances, thought disturbances and sleep difficulties. Her clozapine dose was maintained at the same dose up until the 16th week of her clozapine therapy. There was no recurrence or a new report of side effects and improvement of sleep patterns were reported by her, but her psychotic symptoms still persists. She continued to have regular psychiatry and surgical team review for her condition.

Discussion

Psychiatric patients have an increased risk for venous thromboembolism (VTE) due to multiple factors such as poor mobility, poor fluid intake, fever and rhabdomyolysis that occurs in neuromuscular syndrome. In the case of Miss CJ, apart from the manifestation of hyper salivation, she was mobile and there were no other features of having side effects of neuroleptic intake. In this case of Miss CJ, who was on treatment of clozapine and had developed venous thromboembolism during the duration of this treatment.

Clozapine, most often than not, is usually reserved for highly indicated scenarios such as treatment-resistant cases or highly suicidal cases. Benefits and risks of clozapine treatment had always been a debate among clinicians in achieving remission among schizophrenic patient. While it is easy to agree that risking potentially fatal side effects among patients with tolerable residual psychotic symptoms is inappropriate, it is not as simple when the psychosis leads to a similar fatality risk in the form of suicidality.

Miss CJ definitely benefitted from the clozapine treatment as she remitted from the positive symptoms of schizophrenia and was free from self-harm act during that duration. It is believed that clozapine appears to reduce mortality in severe schizophrenics, mostly by decreasing suicide rates. The venous thromboembolism (VTE) complication suffered by Miss CJ was a hindrance to her recovery process.

As more and more case are reported to associate clozapine with venous thromboembolism (VTE), it is important to be thorough in the screening of deep vena thrombosis (DVT) risk among the target group of patients planned to be initiated on clozapine therapy. Some recent evidences supported the benefit of screening for DVT risk among patient treated with second-generation antipsychotics, including clozapine. Psychiatric patients are identified to be having an increased risk of venous thromboembolism with the use of clozapine so the following of prophylactic measures should be considered. First, avoid strict bedrest or immobility; and an increased amount of exercise for most patients. Also, sufficient hydration is of
importance. Second, complaints such as swelling, pain or discoloring of the leg, chest pain or dyspnea merit special attention. Conducting physical examinations focusing on these complaints is essential. Lastly, the implementation of other deep venous thrombosis prophylactic measures (i.e. placement of elastic stockings, use of pneumatic compression or administration of subcutaneous heparin) should be considered in high risk patients [9].

Given the significance of the ‘love-hate’ relationship of clozapine therapy, empowering patients with the decision making capacity, while allowing them to choose the best option of treatment for themselves is definitely the way to go forward.

References


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