SAS Journal of Medicine
Abbreviated Key Title: SAS J Med
ISSN 2454-5112
Journal homepage: https://saspublishers.com

OPEN ACCESS

Medicine

Deep Venous Thrombosis in a Patient with Neuroleptic Malignant Syndrome Induced by Aripiprazole: A Case Report

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DOI: https://doi.org/10.36347/sasjm.2024.v10i08.020 | **Received:** 15.05.2024 | **Accepted:** 22.06.2024 | **Published:** 28.08.2024

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Abstract **Case Report**

Neuroleptic malignant syndrome is a psychiatric emergency. It is a rare and potentially fatal drug reaction associated with the use of antipsychotic agents. The association between conventional antipsychotics and deep veinous thrombosis has been reported in various case reports and observational studies and several factors have been incriminated. We report here a case of neuroleptic malignant syndrome due to an atypical antipsychotic (aripiprazole) associated with deep venous thrombosis of the lower limb.

Keywords: Deep Venous Thrombosis, Neuroleptic Malignant Syndrome, Aripiprazole, Drug Reaction.

INTRODUCTION

Neuroleptic malignant syndrome is a rare and potentially fatal drug reaction associated with the use of antipsychotic agents, with a mortality risk of 5.6% [1]. The pathogenesis involves blockade of central dopamine receptors leading to hyperthermia, autonomic imbalance and parkinsonian symptoms such as rigidity. The incidence of neuroleptic malignant syndrome has been estimated at between 0.02% and 3.43% in patients receiving antipsychotic agents [2]. Symptoms generally appear within the first two weeks of starting treatment.

Antipsychotic agents are a group of drugs with a wide range of indications used mainly for the treatment of psychotic symptoms and are recommended for treating schizophrenia, bipolar disorder, resistant depression, autism spectrum disorder [3].

The association between conventional antipsychotics and venous thrombophlebitis has been reported in various case reports and observational studies [4, 5]. In addition to antipsychotics, neuroleptic malignant syndrome is thought to increase the risk of deep venous thrombophlebitis.

We report here a case of neuroleptic malignant syndrome due to an atypical antipsychotic (aripiprazole) associated with deep venous thrombosis of the lower limb.

CLINICAL VIGNETTE

Miss S.B, aged 37, diagnosed with schizophrenia and admitted to hospital for agitation during which she hit her mother by threatening her with a knife with a persecutory and mystico-religious delusion and auditory hallucinations.

The disorders began 14 years ago with a change in behaviour involving withdrawal, isolation and irritability, followed by aggression. She began to report auditory hallucinations, saying that evil spirits were talking to her and insulting her. She was admitted to hospital for the first time and put on amisulpride with good clinical improvement, and the diagnosis of schizophrenia was made. Her condition remained stable for about 9 years, but changed completely about 9 months before she was admitted to hospital. She allegedly met a man she wanted to marry and stopped his treatment, which had been causing her amenorrhoea for some time; she became very aggressive and persecuted her mother, and her condition got worse and worse until she began threatening to kill her with a knife.

On admission to hospital, the patient was started on Aripiprazole 20mg/day and then 30mg/day. The patient had no notable medical or surgical history. Prolactin levels were 87ng/ml. The patient's condition remained unchanged, with fewer agitated episodes. 10 days after initiation of aripiprazole, she developed muscle rigidity, hypersalivation and a fever of 38.3 with

tachycardia. Antipsychotic treatment was stopped and she was put on diazepam. All the laboratory tests were normal except for a creatine kinase level of 6792 U/L.

The patient's psychological state worsened. She became more aggressive, hallucinating most of the time, and was put in the isolation room several times, but without restraint. On the fifth day after the onset of neuroleptic malignant syndrome, the patient presented with swelling of the left leg with redness, heat and pain. Doppler studies revealed deep vein thrombosis, and the patient was put on heparin therapy followed by anticoagulant treatment (acenocoumarol). Given the lack of improvement and the difficulty of taking this anticoagulant because of her psychological state, the patient was put on another anticoagulant treatment (Rivaroxaban) with clinical and paraclinical monitoring.

About 3 weeks later, the patient's condition improved, her creatine kinase decreased, and she was put on olanzapine with good clinical improvement and disappearance of her auditory hallucinations. At discharge, she was stable and discharged on Olanzapine 20mg/d and Rivaroxaban with regular appointments.

DISCUSSION

Neuroleptic malignant syndrome is a psychiatric emergency characterised by fever, muscle rigidity, altered mental status and rhabdomyolysis. The symptoms of neuroleptic malignant syndrome have often been described in relation to typical antipsychotics, but it has been debated whether it also applies to atypical antipsychotics. A review by Trollor [6], suggests that most antipsychotics (whether typical or atypical) present in the same way.

However, Belvederi Murri *et al*., [7], considered that the neuroleptic malignant syndrome induced by aripiprazole, highlights some key differences from other atypical antipsychotics: rigidity and altered mental status are universally present; fewer autonomic signs such as hyperpyrexia, excessive sweating and tachypnoea; more autonomic symptoms such as nausea and vomiting; lower creatine kinase peaks; and less severity and duration of neuroleptic malignant syndrome.

Our patient in this study developed neuroleptic malignant syndrome after 10 days of aripiprazole administration, with marked rigidity and deterioration of mental status with worsening agitation and auditory hallucinations. Contrary to the literature [7], however, she presented with high fever and tachycardia, as well as elevated creatine kinase levels of over 6000 U/L.

The association between conventional antipsychotics and venous thrombophlebitis has been reported in various case reports and observational studies. A recent meta-analysis [8], attempted to establish the risk of deep vein thrombosis and pulmonary embolism in antipsychotic users compared with non-users. This study suggests that exposure to antipsychotics increases the risk of deep vein thrombosis. These results further implicate antipsychotics as an independent factor contributing to deep vein thrombosis. Both first-generation and second-generation antipsychotics were associated with this risk. Subgroup analyses of this same study suggest that new users of antipsychotics are more likely to develop deep vein thrombosis. The use of haloperidol, risperidone, olanzapine or prochlorperazine significantly increased the risk of thrombosis, but not that of chlorpromazine, quetiapine or aripiprazole. This is different from our case, which was treated with aripiprazole.

The mechanism of the risk of deep vein thrombosis and exposure to antipsychotics remains unclear. Both psychotic disorders and antipsychotics may play a role in the development of thrombosis. The literature explains that possible mechanisms include immobilisation, metabolic syndrome, increased antiphospholipid antibodies and hyperprolactinaemia. Immobilisation leads to circulatory stasis, which, as one of the components of Virchow's triad, is a well-known risk factor contributing to VTE. Many types of antipsychotics have been indicated to have a sedative side effect, which can lead to immobilisation [8]. In addition, physical restraint and catatonia during neuroleptic malignant syndrome may promote vascular injury and hence deep vein thrombosis. Dehydration, fever and rhabdomyolysis may each lead to a systemic hypercoagulable state and altered mental status. In our study, the patient already had hyperprolactinemia at 87ng/ml and was isolated for her agitated seizures, which would have favored circulatory stasis.

Metabolic syndrome and obesity may contribute to increased platelet activity via the inflammatory process. Hyperactive coagulation plays a direct role in platelet aggregation, which has been reported in antipsychotic users [9]. An increase in platelet aggregation has been observed after treatment with clozapine [10], but a contradictory result was suggested in an in vitro study, showing that this issue remains controversial.

Close monitoring of any manifestations (swelling, pain, redness) of venous thrombophlebitis should be performed routinely to ensure early detection and appropriate intervention.

In our case, the reason for the patient's deep vein thrombosis could involve several factors. It could be due to a combination of neuroleptic malignant syndrome, dehydration, immobility, hyperprolactinaemia and the atypical antipsychotic drug (aripirazole).

CONCLUSION

The risk of deep vein thrombosis associated with neuroleptic malignant syndrome and atypical

antipsychotic drugs is well established. Clinicians need to be fully aware of the risks in patients presenting with neuroleptic malignant syndrome. More studies seem necessary to consider standard prophylaxis against deep vein thrombosis in all patients with neuroleptic malignant syndrome at increased risk of developing thrombosis.

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