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Case Report

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Sudden Increase of Antipsychotics and Induction of Deep Vein Thrombosis

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ABSTRACT

Introduction: Antipsychotics (APs) can induce pathological blood clotting. Deep Vein Thrombosis (DVT) is a common type of Venous Thromboembolism (VTE) and a significant cause of morbidity and mortality worldwide. First or second generation APs have been specifically correlated with an increased risk of thromboembolism.

Case presentation: We report a case of a bipolar female patient who developed DVT following an increase in her daily dose of APs (olanzapine and chlorpromazine).

Conclusion: Physicians in other medical fields, including internal medicine and surgery, should be trained about the complication of DVT induced by APs.

Introduction

Antipsychotics (APs) can induce pathological blood clotting via sedating and immobilizing patients or by causing metabolic syndromes, such as obesity. Such symptoms can be missed in psychiatric settings due to the sedation of patients and the psychopathological symptoms exhibited.

Venous Thromboembolism (VTE) is an important cause of morbidity and mortality worldwide, and almost a third of patients diagnosed with VTE experience long-term consequences [1]. Deep vein thrombosis

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(DVT) is a common type of VTE that has a weighted mean incidence of approximately 5 per 10000 person-years [2] and a mortality rate of above 15% within three months of diagnosis (including pulmonary embolism) [3]. First or second generation APs have been specifically correlated with an increased risk of thromboembolism [4]. A recent meta-analysis estimated that there was a nearly 50% increased risk of VTE among people who took APs [1]. However, the underlying mechanisms have remained mainly unknown [1].

Numerous plausible mechanisms have been proposed as potential novel explanatory pathways for this increase in thrombotic events. These mechanisms include the induction of metabolic abnormalities, such as dyslipidemia and hyperhomocysteinemia, or drug-induced weight gain. Other causes include venous stasis, a sedentary lifestyle caused by drug-induced sedation, antiphospholipid antibodies, which are increased by chlorpromazine, and higher platelet aggregation through the activation of the serotonergic system. Finally, there is hyperprolactinemia through the activation of several coagulation markers, such as antithrombin III, adenosine diphosphate, fibrinogen, and prolactin, which is regarded as a potentially procoagulant hormone [1].

Olanzapine [5] and chlorpromazine also cause VTE by similar mechanisms discussed above. High doses and the concomitant use of multiple antipsychotic therapies also increase the risk of thrombosis [4].

We report a case of a bipolar female patient who developed DVT following an increase in the daily dose of olanzapine and chlorpromazine. No personal or family history of DVT was present. Her condition suggested a possible association between APs and DVT.

Case Reports

This patient was a 58-year-old woman from a northern city in Iran; she was uneducated and unemployed. She was on medication for bipolar disorder from 33 years ago and took olanzapine and chlorpromazine, from at least one year ago. She had been undergone left-foot graft surgery about two months before the current admission to repair surgical scar of her last year left-sided foot melanoma surgery. After the graft surgery, she developed a new mania episode. It resulted in an increase in the dose of her antipsychotic drugs from 2 weeks before the current admission. Then she had swelling and tenderness in the lower extremity for about three days before the present admission to the hospital.

Her right lower limb had become tense and edematous three days before she was brought to a general hospital by family members in August 2017. They complained about her drowsiness, slurred speech, and ten-

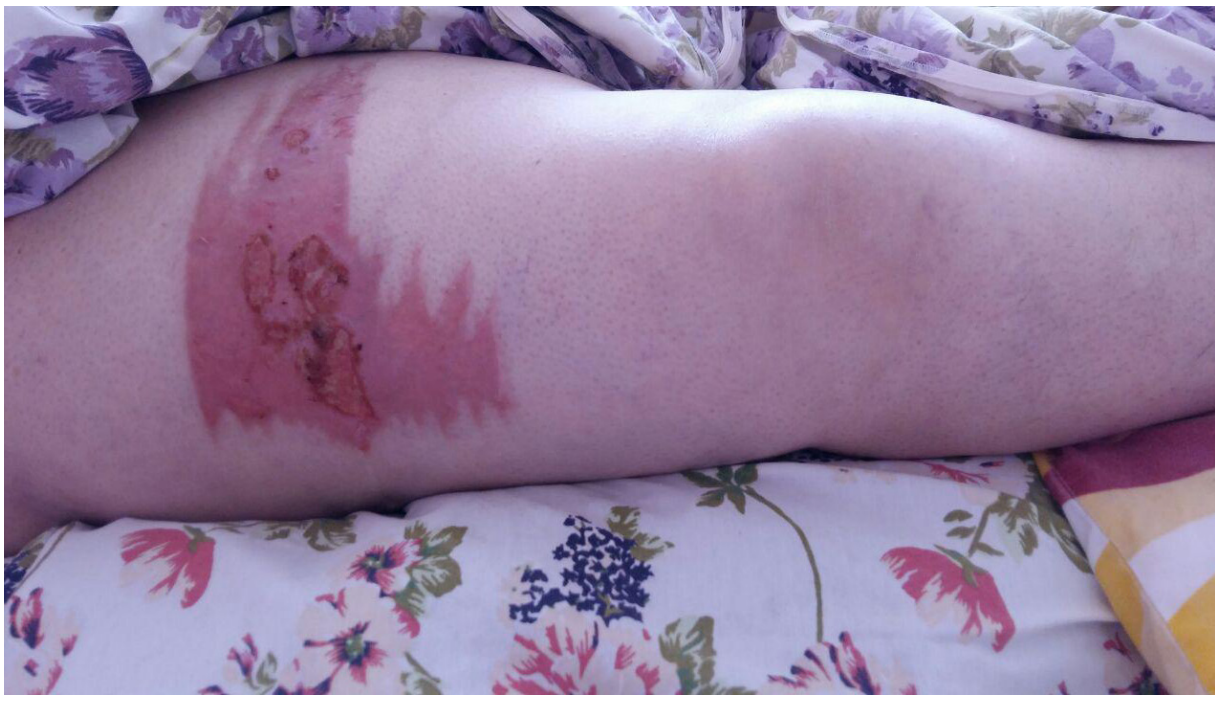

Figure 1. Tense and edematous right lower limb

derness, and edematous limb (Figure 1). Because of her medical history of using AP drugs, psychiatric consultation was requested. During the initial psychiatric consultation, the psychiatrist found that she had a manic episode recently (2 weeks ago), so her psychiatrist had increased the dose of olanzapine from 15 mg/d to 30 mg/d and added 75 mg/d chlorpromazine to valproate sodium. The patient became sedated and had slurred speech. Two weeks after increasing the drug doses, her right leg became edematous and tender. We found that the patient had slurred speech and was rigid, disoriented, and drowsy. Therefore, the proposed diagnosis was AP-induced DVT. Her doses of olanzapine and chlorpromazine were reduced, and the sodium valproate dose was increased to control her unstable mood. The patient showed a favorable response to this treatment, and after one day, her slurred speech improved, and her tense limb became relaxed. After two days, her limb edema improved.

Discussion

There are reports of VTE in patients with psychiatric disorders who were under treatment with second-generation antipsychotics [6-8]. In these cases, patients with high-risk factors for thromboembolism (such as older age, especially older than 40 years, immobility, obesity, smoking, high levels of factor VIII and mild hyperhomocysteinemia and factor V Leiden mutations) were reported to develop VTE in the first year, especially in the first three months, and mostly in the first month after starting or increasing antipsychotic doses [6-8].

According to the meta-analysis of Barbara et al., antipsychotic use was associated with a 50% increased risk of thromboembolism [8]. Another meta-analysis suggests that low-potency antipsychotics are more likely to increase the risk of thromboembolism [8].

Other factors, however, have also been implicated in increasing the incidence of thromboembolism in antipsychotic users. These factors include the period after initiation or increase of the antipsychotic dose, antipsychotic class, higher dose of the antipsychotic, use of several antipsychotics, and antipsychotic injections [8]. Also, the effect of antipsychotics on weight gain and lethargy [7] have been identified as risk factors for VTE.

According to the study of Dijkstra et al., second-generation antipsychotics, such as olanzapine, are associated with a high risk of VTE. This relationship can be explained by the risk factors such as significant weight gain and lethargy that both of which are olanzapine complications. There is no valid risk score for the detection of psychiatric patients who benefit from VTE drug prophylaxis. In patients treated with a second-generation antipsychotic such as olanzapine who develop VTE, olanzapine discontinuation may be necessary based on individual risk profiles, psychotic symptoms, and antipsychotic treatment options [7] .

Masopust et al. reported ten patients with VTE risk factors that developed VTE during treatment with olanzapine, and 6 of them developed VTE 6 months after starting olanzapine. The mean dose of olanzapine was 14.5 mg/d [8].

Rarrick and colleagues also showed that antipsychotic use was associated with a significant increase in the risk of VTE. They showed that most VTE happened within the first year of initial exposure, especially in the first 31 to 90 days of antipsychotic initiation [6].

Other studies reported that the risk of VTE was highest in the first three months after initiating antipsychotic therapy. Masopust also found that the highest risk of VTE development exists in the early stages of antipsychotic treatment [8]. In our case, VTE occurred two weeks after increasing antipsychotic doses (olanzapine and chlorpromazine).

The high number of cases of VTE during treatment with olanzapine maybe because it is a very common antipsychotic drug [8].

In the present study, the patient had risk factors for VTE development, such as olanzapine consumption, increased antipsychotic dose, use of several antipsychotics, immobility, and antipsychotic-induced lethargy. She developed VTE symptoms after approximately two weeks of increased antipsychotic dose.

In prescribing antipsychotics for patients at high risk of developing VTE, the physician should be careful after initiation or increasing dose of antipsychotics and monitor the patient for the occurrence of VTE. High-risk patients and their families should be educated about the signs and symptoms of VTE. The risk of VTE should be measured in high-risk patients to take preventive measures. Whenever clinical signs of VTE occur, the diagnosis should be confirmed or rejected immediately by imaging and laboratory tests [8].

Neuroleptics can induce DVT, particularly when there is a sudden increase in the dose or the concomitant use of multiple APs. This complication should be considered

as an essential and indispensable aspect of training for psychiatric and surgical residents in Iran. There is also a need for training in other medical fields, including internal medicine and surgery, about this complication (APs can induce DVT). Besides, the presence of consultation-liaison psychiatry in general hospitals may aid in the correct handling of patients who took APs and admitted because of DVT.

Ethical Considerations

Compliance with ethical guidelines

Informed consent was obtained from the patient for the publication of this report.

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Conflict of interest

The authors declared no conflict of interest.

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