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RESEARCH ARTICLE

VENOUS THROMBOEMBOLISM AND ANTIPSYCHOTICS: A CASE REPORT

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Abstract

A possible association between venous thromboembolic disease and the use of antipsychotics has been suggested since the 1950s following the introduction of phenothiazines. Several case studies have supported the idea of increased risk of deep vein thrombosis for those on antipsychotics, but the relative impact of this risk factor remains unclear. Deep vein thrombosis is often the result of a combination of several risk factors. The direct implication of a molecular action of antipsychotics began to be considered after several publications illustrating cases of deep vein thrombosis of the lower limbs and serious pulmonary embolism, paradoxically occurring in young psychiatric patients free from any other risk factors. Many hypotheses have been mentioned to explain the mechanisms of occurrence of thromboembolic events: neuroleptics can induce sedation and weight gain indirectly promoting the thromboembolic risk by reducing mobilization; they may also be responsible for an increase in anti-phospholipid antibody levels, increased platelet aggregation, hyperhomocysteinemia, an increase in serotonin and prolactin levels as well as peripheral vasodilation (responsible venous stasis) thus promoting the occurrence of thromboembolic events. We discuss the role of antipsychotics in the etiopathogenesis of deep vein thrombosis through a literature review as well as a clinical case of a young patient with a schizoaffective disorder who presented deep vein thrombosis on antipsychotics during hospitalization.

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Introduction:-

Deep vein thrombosis is a multifactorial disease characterized by a multitude of risk factors favoring its occurrence. Among these factors, the iatrogenic and especially medicinal factors which remain the most easily avoidable, however quite difficult to prove and establish. [1]

Patients with mental illness put on antipsychotics have a higher risk of developing venous thromboembolism compared to the general population. [2]

VTE venous thromboembolism is a serious and life-threatening condition. Manifestations of VTE include deep vein thrombosis (DVT) and pulmonary embolism (PE). Considering the importance of this condition, considerable sums are spent on treatment in European and North American countries. VTE affects approximately 1.0 to 1.8 people per 1,000 per year [3]. The incidence increases exponentially with age and the risk increases considerably in

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people over 40 [2]. Many studies suggest an association between the use of antipsychotics and the occurrence of venous thromboembolism, which is often linked to a significant risk of disability or death. [4] Since chlorpromazine was introduced to the market in the early 1950s, the use of antipsychotics has been associated with venous thromboembolism (VTE) in several reports. Over the past decade, the evidence has been reinforced by extensive epidemiological studies. It is not yet known whether all antipsychotics increase the risk of VTE or whether the risk is limited to certain drugs. [5]

Venous Thromboembolism and antipsychotic cases published in Morocco are rare. The objective of our work is to discuss through a clinical vignette, based on data from the literature, the role of antipsychotics in ethiopathogenesis in VTE.

Patient and Observation:-

Mr S.T is 48 years old, single, without profession, native and living in Kenitra. He comes from an above averagesocio-economic level. He was admitted to the Arrazi psychiatric university hospital for management of psychomotor excitement, verbalization of delusional remarks and insomnia, falling within the framework of a schizoaffective disorder according to the criteria of DSM 5 [6]. This evolved over 25 years following a therapeutic gap.

Mr S.T observed his treatment with Aripiprazole 15mg per day and sodium Valproate 2 g per day for 3 months, before stopping a month before his admission. He became insomniac, very excited, logorrhic with a verbalization of delusional words of persecution centered on his father, to whom he attributed all his misfortunes. During his hospitalization, he was put on treatment with Risperidone 8 mg per day and sodium Valproate 2 g per day.

During his hospitalization the patient presented a hot, red and hyper-painful swelling of the left leg up to the thigh. Ultrasound Doppler confirmed deep vein thrombosis and he began treatment with Enoxaparin and Acenocoumarol with strict clinical and biological monitoring. Risperidone has been implicated in this Thrombosis after elimination of the other etiologies (Table 1) and was gradually replaced by Amisulpride in combination with sodium valproate. The patient gradually improved after his psychiatric stabilization and regularly attended aftercare appointments.

Discussion:-

Based on the clinical studies analyzed, the main risk factors for venous thromboembolism are the duration of treatment and patient-related factors, such as gender, age, body mass, and physical activity. [5, 1]

During a continuous surveillance period in Germany, which assessed severe adverse drug reactions during treatment on a total of 264,422 hospital patients who were treated with antipsychotics (AP) and followed from 1993 to 2011 in 99 psychiatric hospitals, events of deep vein thrombosis (DVT) were reported for 89 hospitalized patients, which corresponds to a rate of 34 cases per 100,000 admissions of hospitalized patients treated with antipsychotics. [7]

A high risk of venous thromboembolism has been observed with certain antipsychotics, with the highest risk for clozapine, olanzapine, and low-potential first-generation antipsychotics. The risk appears to be correlated with the dosage. The elderly, who mainly use lower doses, do not have an increased thromboembolic risk to the same extent as younger patients. [1]

Clozapine users had the highest thromboembolic risk, and slightly increased risks noted for users of ziprasidone, Chlorpromazine, Haloperidol, Risperidone and Olanzapine. Quetiapine and Aripiprazole users were not at increased risk. The risk of PE increased with higher doses. [8]

In a study from the WHO International Adverse Drug Reaction Database in 2008, a total of 754 suspected cases of venous thromboembolism related to antipsychotics were reported.

After applying a data mining technique to this database, a robust association between venous thromboembolism and 2nd generation antipsychotics was found. The occurrence of venous thromboembolism has been reported more frequently during treatment with Clozapine, Olanzapine, Sertindole and Zuclopenthixol than during treatment with other antipsychotics. [9]

So far, the biological mechanisms responsible for this possible adverse drug reaction have not been found, but several hypotheses have been put forward. For example, antipsychotics such as Olanzapine and Risperidone, which are antagonists of 5HT₂ receptors, can induce an increase in serotonin which in turn could cause increased aggregation of platelets, thereby increasing the risk of thrombosis. [1,10]

The underlying biological mechanisms explaining the association between antipsychotic drugs and the risk of thromboembolism are largely unknown. Several hypotheses have been proposed, such as body weight gain, sedation, platelet aggregation, increased levels of antiphospholipid antibodies, hyperprolactinemia and hyperhomocysteinemia. The risk of thromboembolism in schizophrenia and other psychotic disorders may also be linked to the underlying disease rather than the drug. [1,10]

In patients with mental illness, the risk of thromboembolism is increased for several reasons. One study found a significantly increased activation of markers of thrombogenesis (sP-selectin, D-dimer, FVIII) in untreated patients experiencing a first episode of psychosis compared to healthy subjects. Thrombogenesis markers continued to be elevated after 1 year of treatment. Antiphospholipid antibodies (APA), especially anticardiolipin antibodies (ACLA), can serve as a marker for autoimmune reactivity, or they can directly interfere with phospholipid metabolism in schizophrenic patients. They can also have prothrombotic effects. Inflammatory markers are also elevated during acute psychosis, which can lead to an increased risk of pathological blood clotting. [1, 11]

Hyperhomocysteinemia, which is also a risk factor for VTE, can occur in patients with mental health problems who also smoke, have poor eating habits, and consume excessive amounts of coffee. [11]

According to a meta-analysis by Barbui et al, exposure to antipsychotic treatment leads to a 50% increase in the risk of thromboembolism. In patients hospitalized in psychiatry and restrained, the degree of risk of venous thromboembolism must be determined so that preventive measures can be taken. Whenever clinical symptoms of venous thromboembolism occur, the diagnosis should be confirmed or excluded immediately by imaging and laboratory tests. [12]

Patients treated with olanzapine and risperidone should be monitored clinically for venous thromboembolism to ensure early detection and intervention, and possible discontinuation of treatment with olanzapine and risperidone should be considered if the diagnosis of venous thromboembolism is established. [13].

In a retrospective cohort study of a database of American hospitals comprising 450,000 users of antipsychotics, the risk of pulmonary embolism increased by a modest but statistically significant amount of 1.2 times compared to non-users. The users of first- and second-generation antipsychotics had comparable risks for the thromboembolic risk.

In patients developing venous thromboembolism, adequate antithrombotic therapy should be initiated and consideration should be given to stopping or changing antipsychotic therapy after eliminating other risk factors (Table 1). It may be relevant to avoid clozapine if possible [10].

Particular attention should be paid to stopping the offending antipsychotic medication in patients with venous thrombosis and replacing it with another antipsychotic medication with a likely lower risk. It is essential that doctors and patients are aware that venous thromboembolism can be an adverse reaction to antipsychotic drug therapy so that the disease is identified early and treated appropriately. [5]

Patients treated with antipsychotics should be evaluated for the risk of venous thromboembolism and, if necessary, appropriate prevention methods (including especially the elimination of modifiable risk factors) should be implemented. In addition, patients should be informed of the scope of prodromal symptoms. [4]

People at high risk using antipsychotics should be advised of the importance of seeking immediate medical attention. Obvious VTE in a patient using an antipsychotic should be managed as soon as possible [14].

Current data do not identify the prothrombotic potential of atypical and conventional antipsychotics or indicate a higher risk of developing venous thromboembolism in treated patients. Due to the complex pathogenesis of venous

thrombosis, large comparative studies would be necessary, allowing the differences in prothrombotic potential of antipsychotics to be identified with precision. [15]

Conclusion:-

Antipsychotics appear to be a risk factor for venous thromboembolism. The general thromboembolic risk relates to the therapeutic procedures and to the mental pathology itself, hence the need for close clinical monitoring, associated with preventive measures, and the need to discuss the risk of VTE with patients before the use of antipsychotics. This can help clinicians and patients safely determine the most appropriate treatment for their psychiatric illness while mitigating potential side effects.

The association between antipsychotics and venous thromboembolism remains questionable. Future studies should be performed to further quantify this association

Competing Interests:

No conflict of Interest.

Table 1:- The main thromboembolic risk factors and etiologies of VTE according to current data: [10].

Clinical factors	Clinical factors Advanced age Hospitalization for acute medical illness Long-haul flights (duration > 4 h) Obesity Pregnancy, including the postpartum period
Drug Causes	Antipsychotics Anti-estrogens Chemotherapy Heparin-induced thrombocytopenia High dose therapy with progestins Hormone replacement therapy Oral contraceptives Vaginal ring for contraception Strontium ranelate Thalidomide and lenalidomide
Medical pathologies	System diseases Antiphospholipid syndrome congestive heart failure inflammatory bowel disease malignant tumors Vaquez disease thromboembolic history Septicemia varicose veins
Surgical factors	Major surgery Orthopedic surgery Trauma or fracture
Hereditary factors	Antithrombin deficiency Dysfibrinogenemia Factor V Leiden mutation Deficit in protein C protein S deficiency Prothrombin mutation 20210A

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