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RESEARCH ARTICLE

THROMBOEMBOLIC COMPLICATIONS IN CHRONIC INFLAMMATORY BOWEL DISEASE

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Abstract

Patients with chronic inflammatory bowel disease (IBD) represented by Crohn disease (CD) and ulcerative colitis (UC) are at higher risk for thromboembolic complications (CTE) which are a major cause of morbidity. They are attributed to a pre-thrombotic state induced by the inflammatory activity of this disease. The thrombotic risk inpatients with IBD is underestimated and thromboprophylaxisis not widely implemented in the clinical practice. Many studies on thromboembolism in the IBD populationhave already been carried out, however the precisepathogenesis is still poorly understood. The aim of our study is to determine the prevalence, risk factors and clinical aspects of thrombosis during IBD.

Introduction:-

Thromboembolism is an underestimated extraintestinalcomplication of IBD patients, which is associated with ahigh morbidity and mortality [19].Patients with inflammatory bowel disease have a 1.5 to 3.5 times higher risk of thromboembolism compared to the population without IBD and the risk is much more prominent during a relapse [20].

Thromboembolic events are a common serious complication of IBD occurring in young patients, the most common site being the deep veins of the leg, pulmonary vessels, and others such as cerebral, hepatic and mesenteric vessels.

The extent of colonic disease has a correlation with thromboembolic risk. Extensive UC and colonic involvement in CD were significantly associated with the development of thromboembolism [23].

The close relationship between inflammation and thrombosis affects the progression and severity of inflammatory bowel disease. The development of thrombosis in IBD is due to the interaction of many inherited and acquired risk factors. Each patient diagnosed with IBD should be evaluated for a personal and family history of thrombosis and for the use of prothrombotic drugs. Although procoagulant factors are increased during the natural course of inflammation, natural anticoagulants and fibrinolytic activity are decreased. Although IBD is accepted as a prothrombotic disease, there is no treatment that can eliminate this risk from daily practice. Patient education is necessary to control important factors, such as long-term immobilization and smoking. Oral contraceptives and hormone replacement therapy should be avoided. Induction of permanent remission of the disease should be the key approach for the prevention of thrombosis. Low molecular weight heparin (LMWH) is the basis of prophylactic therapy, which reduces the risk of thrombosis by 50% [21-22]. LMWH prophylaxis should be given to all IBD patients hospitalized for an attack of the disease or for surgery. Long-term or even lifelong anticoagulant therapy

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should be planned in case of insufficient disease control, recurrent VTE attacks, positive thrombophilia tests, or thrombosis in vital veins.

Materials And Methods:-

This is a descriptive retrospective study carried out over a period of 16 years (2005 - 2021) that included all known or newly diagnosed IBD patients who have developed venous or arterial thrombosis (16 patients)confirmed by Doppler ultrasound, CT angiography or MRI.

Results:-

A total of 887patients were included. A thromboembolic accident occurred in 16 patients, i.e., a prevalence of 5.33%; they were 11 women and 5 men with a sex ratio = 2.2 and an average age of 42.19 years (17-74 years).

7 patients had Crohn's disease: 4 ileo colonic and 3 colonic (fistulizing in 3 cases, stenosing in 2 cases and luminal in 2 cases).9 patients had ulcerative colitis (pancolonic in 7 patients, rectal in 1 patient and left colic in 1 patient).The mean time between the diagnosis of IBD and the onset of the thromboembolic complication was 28.42 months [1 week-12 years].

1 patient had hypertension, 1 patient was diabetic, 1 patient was a smoker and no patient was overweight. There was no background of pregnancy, childbirth or oral contraception in the 11 female patients, no patient was in the postoperative period.

It was a deep thrombosis of the lower limbs in 10 cases (62.5%), isolated in 5 cases (unilateral in 4 cases and bilateral in 1 case), associated with a pulmonary embolism in 3 cases, and a thrombosis cerebral venous thrombosis in 2 cases, renal thrombosis in 1 case (6.25%), a myocardial infarction in 1 case (6.25%) and an isolated cerebral venous thrombosis in 4 cases (25%).

At the time of thrombosis onset: 15 patients (93.75%) had active IBD, 11 patients (68.75%) were under corticosteroid therapy, 3 patients (18.75%) were on 5-ASA. Anemia was observed in 14 patients (87.5%), hyperleukocytosis was observed in 3 patients (18.75%), hyperplaquettosis was observed in 4 patients (25%), CRP was high [18-232mg/l]in 15 patients (93.75%) and hypo albuminemia [13-29mg/l] was observed in 15 patients (93.75 %).

Curative heparin therapy with low molecular weight heparin was started in all patients as soon as the thromboembolic complication was diagnosed with relay by Vitamin K antagonists(VKAs) in 15 patients and by direct oral anticoagulants (DOACs) in one patient.

Patients' outcome was good in 12 patients (75%), 4 patients died (25%) including 3 from cerebral venous thrombosis and one patient from pulmonary embolism.

Presentation of the results

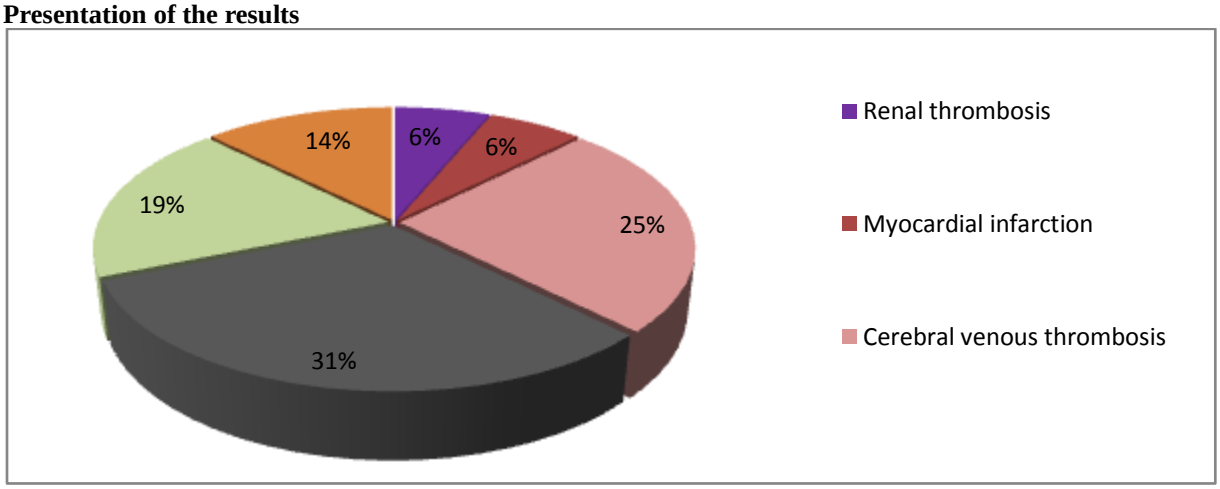
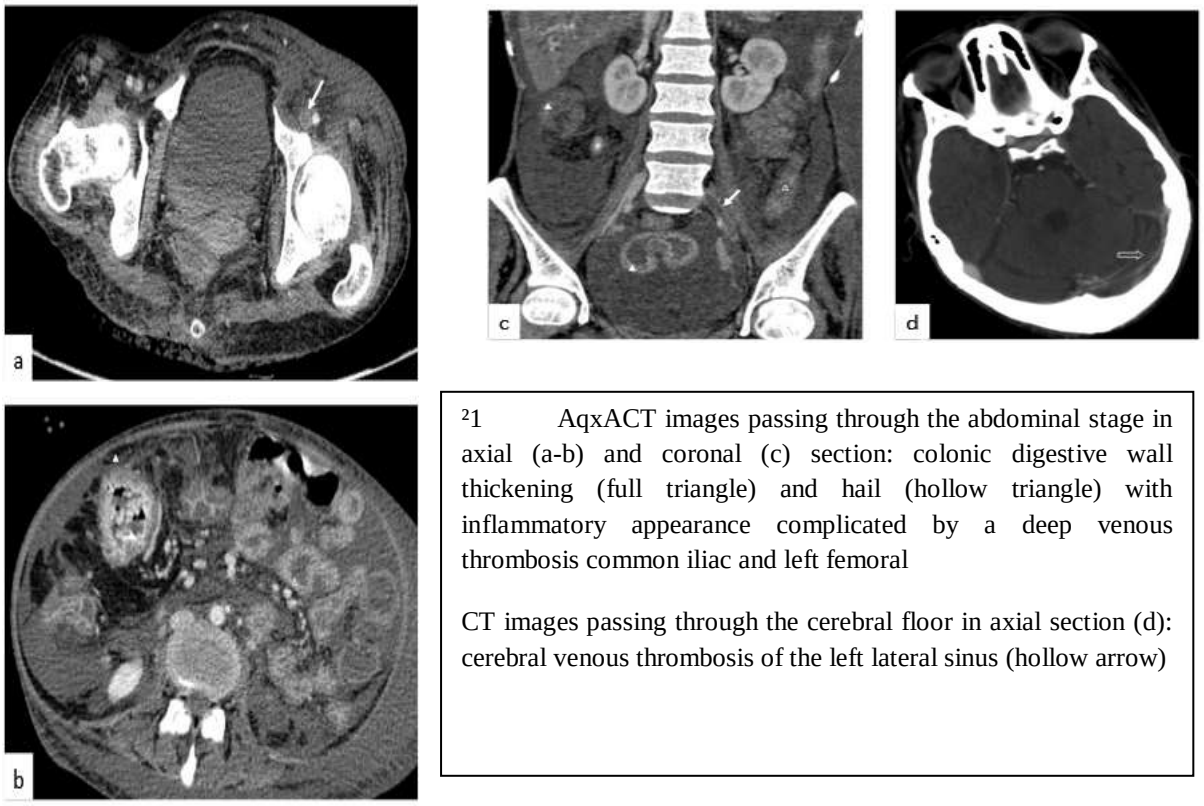


Figure 1:- Clinical Aspects Of Thromboses During Ibd.

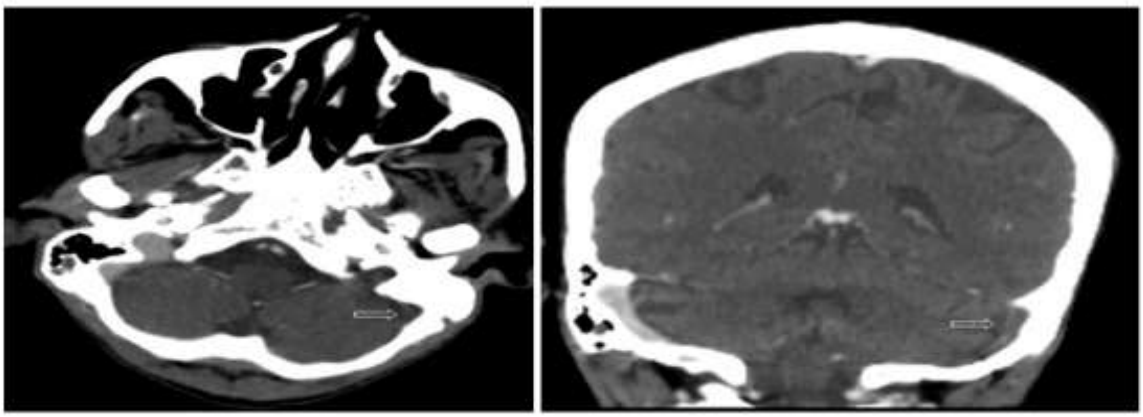
Table 1:- Characteristics of diseases with ibd who have developed a thromboembolic complication.

Parameters	Characteristics	
Averageage	42.19	
Sex ratio	2.2	
IBDProfil	Crohn Disease	43.75%
	Ulcerative colitis	56.25%
Diseaseactivity	93.75%	
anemia	87.5%	
hyperleukocytosis	18.75%	
hyperplatelet	25%	
High CRP	93.75%	
hypoalbuminemia	93.75%	
Patients on corticosteroid therapy at the time of discovery of thrombosis	68.75%	



[21] AqxACT images passing through the abdominal stage in axial (a-b) and coronal (c) section: colonic digestive wall thickening (full triangle) and hail (hollow triangle) with inflammatory appearance complicated by a deep venous thrombosis common iliac and left femoral

CT images passing through the cerebral floor in axial section (d): cerebral venous thrombosis of the left lateral sinus (hollow arrow)



CT images passing through the cerebral floor in axial (a) and coronal (b) section: cerebral venous thrombosis of the left lateral sinus extended to the jugular golf course (hollow arrow)

Discussion:-

In addition to digestive lesions, chronic inflammatory bowel diseases induce several extra-intestinal manifestations, including thromboembolic complications.

There is an increased risk of thromboembolism in patients with IBD, with a prevalence varying between 1.3 [1] and 7.7% [2]. Furthermore, a thromboembolic risk 3.5 times higher compared to the general population [3] and compared to controls [4]. In our study, we found a prevalence of 5.3% of CTE during IBD but the real incidence is surely underestimated since these complications are often asymptomatic and unrecognized.

The median age of onset of thromboembolic complications in patients with IBD is 40 years, ranging from 22 years to 61 years [5]. In our study the mean age was 42.19, it would seem that these thromboses affect the young population [6]

Regarding topography, thrombosis is mainly venous dominated by deep vein thrombosis of the lower limbs and pulmonary embolism. The arterial thrombosis is exceptional most often following surgery [3, 4], which has been observed in our study where MI occurred in one of our patients. Less frequent sites of thrombosis, namely cerebral [1], retinal, portal mesenteric or gonadal thrombosis have also been described. In our study, deep vein thrombosis of the lower limbs was dominant. However, we noted cerebral venous thrombosis (CVT) in six patients (isolated in 4 cases and associated with DVT in 2 cases).

Moreover, thromboembolic complications seem to be associated more with UC than with Crohn's disease [7], which has been observed in our patients.

The pathophysiology of thromboembolic diseases during IBD remains unclear. However, there is a prothrombotic state following abnormalities of primary hemostasis, activation of coagulation and hypofibrinolysis [8]. Inflammation seems to play a primary role in the appearance of this hypercoagulability. Therefore, when IBD is active, several abnormalities of hemostasis are observed including thrombocytosis, an increase in the level of coagulation factors I, V, VIII and a decrease in the level of antithrombin III [8]. In our study, thrombocytosis was observed in 25% of patients.

Moreover, clinical studies show that at least 60% of patients with IBD have an active disease when thromboembolic events occur [1, 4, 6, 9, 10] and that these accidents are correlated with IBD activity [2]. This led Miehsler et al. [4] to conclude that thromboembolic disease is a specific complication of IBD because neither rheumatoid arthritis being a chronic inflammatory disease nor celiac disease being a chronic bowel disease was at risk increased thromboembolic complications [4]. However, in some cases, thromboembolic events may precede the diagnosis of IBD [2]. What was observed in our study where IBD was active at the time of CTE in 93.75 of patients
The formation of a thrombosis involves the association of several acquired or genetic prothrombogenic factors [7,11]. Besides the intestinal inflammation which seems to be the most determining. There are other acquired risk factors such as oral contraception, prolonged immobilization, surgery, corticosteroid therapy, dehydration, hyperhomocysteinemia and constitutional such as antithrombin deficiency III, protein C, S, PRCA and the prothrombin gene mutation [12]. Their prevalence is not higher in patients with IBD, but their presence seems to increase the risk of thromboembolism [12].

Some studies have suggested that intestinal protein losses [13] contribute to the constitution of thrombosis by loss of natural anticoagulant factors such as antithrombin III, protein C or protein S [13,14]. In our study, a hypo albuminemia was observed in 93.75% of our patients. However, the thrombophilia assessment was not studied given the retrospective nature of the data collection and the incomplete and non-standardized nature of this assessment.

All the patients who were hospitalized in our department for management of IBD received preventive heparin therapy based on LMWH in accordance with the recommendations [15], which did not prevent the occurrence of a thromboembolic complication in 5 of our patients. In addition to this preventive anti-coagulation, the reduction of the thromboembolic risk during IBD could be ensured by the control of the activity of IBD, the correction of malnutrition and vitamin deficiencies, smoking cessation and stopping oral contraception [16].Furthermore, there is

no consensus concerning the curative treatment of thrombophlebitis during IBD. This is based on heparin therapy (continuous or low molecular weight heparin, or fondaparinux) followed by vitamin K antagonists for a minimum period of 3 months [17,18]. Long-term treatment may be considered in some cases.

Conclusion:-

The prevalence of thromboembolic complications in our series was 5.33%. DVT of the lower limbs was the dominant condition. The pathophysiology of the occurrence of thromboembolic complications during IBD is multifactorial. it seems to be linked above all to the activity of the disease, hence the benefit of a systematic preventive anti-coagulation in all patients with a relapsing IBD.

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