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RESEARCH ARTICLE

TWO CASES OF UNUSUAL LOCATIONS OF VENOUS THROMBOEMBOLISM, DUE TO FACTOR VIII EXCESS.

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Abstract

The genesis of venous thrombosis is multifactorial, requiring an etiological assessment, when the usual risk factors are absent. Thrombophilia can then be a frequent, acquired or congenital cause and becomes responsible for a state of hypercoagulability. The excess in antihemophilic factor A or factor VIII is part of the hereditary etiologies, which are not systematically sought in the case of unexplained thrombosis. This is due to its rarity compared to other more frequent causes (deficiency of protein C, protein S and antithrombin). At the Avicenne hospital in Marrakech, we received 2 women with thromboses of rare localizations: renal and cerebral. Classical etiological investigations had not revealed the cause. Only the dosage of the factor showed significantly increased levels, apart from any physiological or pathological situations that could explain it, thus making the singularity of these two observations. Although treatment with the acute phase is well codified, the maintenance of anticoagulation in the long term remains questionable.

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Introduction:-

Venous thrombosis is a multifactorial disease (Virchow, 1865). According to Virchow, it can be due to an injury to the vascular wall, an alteration in the blood composition or its flow. The hemostatic equilibrium can be changed in certain congenital or acquired conditions and becomes responsible for a hypercoagulable state, called thrombophilia. The first form of thrombophilia, antithrombin deficiency, was described in 1965. Other factors were identified later on, including an excess of factor VIII. We discuss the cases of two women with unusual locations of venous thromboembolism: cerebral and renal venous thrombosis, both were found to have an isolated excess of factor VIII activity in the absence of any other hemostatic abnormalities.

Observation 1:-

A 43-year-old woman, type 2 diabetic under insulin therapy, admitted to the hospital in 2012 for a total hematuria, left-sided low backpain and fever.

On physical examination, the patient had a sensibility in the left flank, a fever at 38°C, and the rest of the exam was unremarkable. These symptoms have begun 45 days earlier and were initially treated as pyelonephritis without any

improvement. Lab tests upon admission showed a microcytic anemia at 11g/dl, a normal platelets and white blood cells (WBC) counts, with a C reactive protein level at 40 mg/l. Renal function as well as the rest blood tests including liver function tests (LFTs), blood glucose and serum protein electrophoresis (SPEP) were normal. Urinary tests showed an important hematuria without leukocytes, and a proteinuria at 0,19 g/24hours.

CT urography revealed a perfusion defect of the left kidney with a thrombus in the renal vein extending to the inferior vena cava, concluding to the diagnosis of left renal vein thrombosis (figure1).

The etiological workup was directed for a potential thrombophilia. Prothrombin time (PT) and partial thromboplastin time (PTT) levels were normal, there was no evidence of a systemic disease, a venous infection of any sort, a myeloproliferative disorder, nor an antiphospholipid syndrome. The levels of antithrombin, C protein, protein S and factor V levels, besides C protein resistance test were all in normal ranges (this in absence of any anticoagulant treatment). The mutation JAK2 as well as the mutation of the prothrombin gene were absent.

While factor VIII activity was elevated to 230% (60% - 150%). The patient had no family history of venous thrombosis. She was treated with heparin, then with vitamin K antagonists for one year. The response to treatment was satisfactory, with no recurrence one year after the initiation of treatment.

Observation 2:-

A 39-year-old patient was admitted to the hospital in March 2012, for an etiological workup of a cerebral thrombophlebitis, that has occurred in 2009. The patient's cerebral venous thrombosis was presented with signs and symptoms of intracranial hypertension, made of headache, vomiting and strabismus with diplopia. Brain magnetic resonance imaging (MRI) concluded to a left lateral sinus thrombosis (figure 2). The patient received anticoagulant therapy for twelve along with corticosteroids without determining the etiology. Clinically, the patient (without any remarkable medical history prior to the episode of 2009) was still suffering from intermittent headaches, her physical examination was normal. The CBC and C-reactive protein were normal. The PT was 78%, and PTT was 35 seconds.

Renal function, LFTs and SPEP were normal. A Control Cerebral MRI was normal. A thrombophilia workup was started: investigations for systemic disease were negative (especially in favor of Behçet's disease), there was no evidence of a local or a regional infection at the time of the thrombophlebitis, no brain tumor or myeloproliferative syndrome. Antiphospholipid antibodies were absent. In absence of any oral anticoagulant therapy, the levels of protein C, protein S, antithrombin III and factor V were normal. The mutation JAK2 as well as the mutation of the prothrombin gene were absent. Only factor VIII activity was elevated to 466%. The patient was given long-term anticoagulant with a marked improvement.

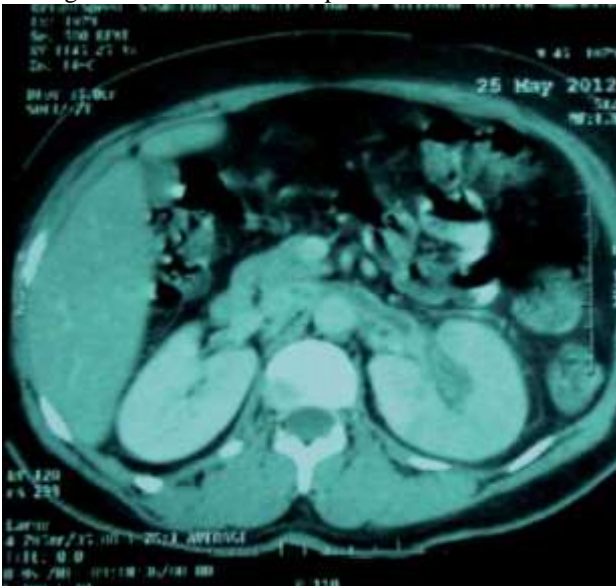


Fig 1:-Left renal vein thrombosis with a uroscanner



Fig 2:- Left cerebral venous thrombosis on an angiMRI

Discussion:-**Renal vein thrombosis:-**

Renal vein thrombosis (RVT) is characterized clinically by an acute lumbar or abdominal pain, with macroscopic hematuria. A palpable kidney could be found on physical examination. RVT may also be insidious, or revealed by proteinuria with or without hematuria. CT scan and MRI confirm the diagnosis (Ives and Daneil, 1991; Ganeval, 1979). In our patient, the clinical presentation was typical, associating fever, low back pain and macroscopic hematuria. The CT urography has allowed to make the diagnosis with certainty and to rule out an acute pyelonephritis.

Cerebral venous thrombosis:-

Cerebral venous thrombosis (CVT) is rare, and occurs commonly in young people. The clinical presentation of cerebral thrombophlebitis is highly polymorphic, associating signs of intracranial hypertension and focal signs when thrombosis gets complicated by a venous infarction. Its onset varies from few days to several weeks. CTVs can mimic an arterial stroke, an abscess, a brain tumor, and even meningitis (Masson and Colombani, 1999; Ameri and Bousser, 1992; Bousser, 1985).

In our case, signs intracranial hypertension were the predominant presentation. Magnetic resonance angiography was decisive in the diagnosis of cerebral thrombophlebitis.

Thrombophilia:-

It was reported that 30% of the patients who had a first episode of venous thrombosis, declare having a first-degree relative with a history of thrombosis (Heijboer et al., 1990). This motivated investigations toward a constitutional thrombophilia, even in the absence of a relevant family history in both patients. The most common etiologies of hereditary thrombophilia (antithrombin deficiency was the first to be described) are: abnormalities of the protein C system with deficiencies of protein C or protein S, and resistance to activated protein C (Comp et al., 1984). Excess antihemophilic factor A or factor VIII is found in 11% of the population. These levels vary with age (increase of 6 IU / dL per decade), sex (women > men), blood group (AB > A = B > O) or ethnic origin (Black > White) (Kamphuisen et al., 2001; Koster et al., 1995). They also increase in some conditions such as inflammation, pregnancy, hyperthyroidism, hepatic or arterial disease.

In Leiden Thrombophilia Study, 25% of patients have high levels of factor VIII (> 150%) with a significantly increased risk of thrombosis (Kamphuisen et al., 2001; Koster et al., 1995). In the first and second observations, factor VIII was elevated: 230% and 466%, respectively. No pathophysiological explanation of these values was made yet. It seems that every increase in factor VIII by 10 IU / dL is accompanied by an increase of the risk thrombotic episodes by 10%. Thus, levels greater than 150 IU / dl are found in nearly 60% of patients with a thrombotic recurrence. The mechanism responsible for increasing the vascular risk is still unknown: elevation of plasma levels of factor VIII may increase the generation of thrombin or induce an acquired resistance to the anticoagulant activity of activated protein C (Kamphuisen et al., 2001; Koster et al., 1995). This isolated excess of factor VIII was retained as the only etiology for these two rare thromboses. After the management of thrombosis in the acute phase, the duration of anticoagulation therapy in thrombophilia must balance the risk of recurrence and the risk of hemorrhage. Constitutional coagulation abnormalities found in these patients has justified their treatments with prolonged anticoagulants.

Conclusion:-

Unusual etiologies of hereditary thrombophilia, including excess factor VIII, should be better known and studied in their pathophysiological and genetic aspects. The workup of venous thrombosis is increasingly improved by testing for different prothrombotic factors. In the presence of any one of these etiologies, a long-term anticoagulation therapy should be indicated, in order to avoid recurrences.

Conflict of interest: none.

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