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Thrombophilia assessment: Experience of the hematology laboratory of IBN ROCHD AMC of Casablanca

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Abstract

Thrombophilia is a condition characterized by an increased tendency to thrombosis. It results from various etiologies often intertwined and involving both hereditary and acquired risk factors. In Morocco, there is a lack of data concerning thrombophilia at the national level and the declaration is not mandatory, the real prevalence of this pathology is impossible to determine. This study concerned patients who presented with thrombosis and whose thrombophilia assessments were carried out at the Hematology Laboratory of AMC Ibn Rochd in Casablanca. 80 assessments were compiled: The main indication that motivated the request for a thrombophilia assessment was DVT in 23 patients (28.75%), followed by ICVA in 20 patients (25%). The results were positive in 51.25% of cases: protein S deficiency was the most frequent (36.25%), anti-phospholipid antibodies were discovered in 2 patients. The diagnosis of venous thrombosis was made in 50 patients (62.5%), and the diagnosis of arterial thrombosis was made in 30 patients (37.5%), of which 20 patients (66.7%) had an ICVA. In our study, the predominant risk factor was PS deficiency unlike literary data in other Western countries which note APCR as the most frequent risk factor. This may be due to ethnic variability, hence the need for a larger multicenter study to confirm these results.

Keywords: Thrombophilia; Venous Thrombosis Arterial Thrombosis; Protein S Deficiency; Prevalence Study

1. Introduction

The term thrombophilia, according to the HAS (High Authority for Health), designates the anomalies or peculiarities of coagulation, which predispose to thrombosis, characterized on one hand by a heterogeneous clinical presentation and on the other hand by biological anomalies responsible for this state of hypercoagulability [4].

Thrombophilia can be constitutional (most often familial or hereditary), or acquired, these factors can be associated with each other and / or with the presence of other risk factors promoting thrombosis, highlighting the multifactorial origin of thrombophilia [5].

The most frequent constitutional abnormalities are primarily a deficiency in coagulation inhibitors, such as: Antithrombin, protein C or protein S, abnormalities such as resistance to activated protein C most often linked to Factor V Leiden mutation. Second, there is the factor II Leiden mutation (the G20210A mutation), an excess of factor VIII and hyperhomocysteinemia. [5].

The discovery of a relatively frequent coagulation abnormality has greater diagnostic profitability for thrombophilia work- ups, and therefore an extension of the indications to the prescription of the laboratory work-up. The impact of

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knowledge of a biological risk factor on patient management is very uncertain, and the available data are often contradictory [6].

The objective of our study is to assess the thrombophilia assessment prescribed by various departments of the Ibn Rochd AMC in Casablanca, and carried out in the hematology laboratory, as well as to specify the latest prescription recommendations.

2. Patients and methods

This is a retrospective descriptive study, which concerned patients in whom a thrombophilia assessment was carried out in the Hematology laboratory of the Ibn Rochd University Hospital Center in Casablanca from the various departments of the AMC, on a three-year period, from July 1, 2016 to June 30, 2019.

Included are all patients, regardless of age and sex, for whom a thrombophilia assessment has been referred to our laboratory.

All patients whose records cannot be found or whose information collected is incomplete are excluded.

To conduct this study, an operating sheet was produced to collect information from patient records at the level of the various departments.

The laboratory diagnosis of thrombophilia in our patients is made based on the results of the simultaneous assay of Protein C, Protein S, Antithrombin, resistance to activated protein C, for constitutional thrombophilia, and / or the search for lupus antibodies prescribed in the context of suspected anti-phospholipid syndrome (SAPL).

After selecting the complete information sheets, we processed the data on the Excel 2010 office. We recorded the information in a table to facilitate analysis and interpretation.

3. Results

During the period of our study, we collected 318 thrombophilia assessments carried out at the Ibn Rochd University Hospital in Casablanca, 80 were included.

The majority of requests, or 21%, were from the neurology service, followed by the hematology service (15%), and the cardiology service with 14% of requests.

The average age is 32.29 years from [1 year to 79 years], with a predominance of the age group] 30-45] years, representing 32% of the study population.

The female sex was the predominant, (29 men, 51 women), with a sex ratio of 0.57.

Our sample is distributed as follows according to the different risk factors in patients with at least one abnormality in the thrombophilia assessment.

The indication for a thrombophilia assessment was made mainly before DVT in 28.75% of cases, APCR in 25% of cases. The indications are distributed as follows:

3.1. Venous thrombosis:

The diagnosis of venous thrombosis was retainedin 50 patients (62.5%), of which 23 patients (46%) had DVT followed by cerebral venous thrombosis in 10 patients (20%).

Table 1 Distribution of the sample according to the type of venous thrombosis

Type of thrombosis	Number	Percentage
Deep vein thrombosis	23	46%
Cerebral venous thrombosis	10	20%

Portal venous thrombosis	6	12%
Jugular vein thrombosis	5	10%
Superior vena cava thrombosis	3	6%
Mesenteric venous thrombosis	3	6%

3.2. Arterial thrombosis

The diagnosis of arterial thrombosis was retained in 30 patients (37.5%), of which 20 patients (66.7%) had a ACVA.

Thrombophilia assessment is considered complete, when there is an assay for AT, PC, PS, the search for APCR / factor V Leiden mutation, and the search for a mutation in the Factor II gene, combining the search for an SAPL according to the age and the clinical context, with the realization of the search for: anti-cardiolipin AC, anti B2GP1 AC and search for a circulating anticoagulant.

The thrombophilia assessment received at the Laboratory was incomplete in all cases, combining the determination of PS, PC, AT and testing for APCR in 38.75% of cases, testing for PS, PC, AT, testing for APCR and LA in 6.25% of cases..

Among the 80 patients included in our study, 37 patients (46.25%) presented no abnormalities in the thrombophilia workup, and 43 patients (53.75%) presented at least one abnormality.

We noted an isolated PS deficiency in 9 patients or (11.25%), an isolated PC deficiency in 6 patients, or (7.5%), and an isolated AT deficiency in 2 patients or (2.5%), a RPC in 2 patients. or (2.5%). The combined PC and PS deficiency was found in 9 patients (11.25%), followed by the combined PC, PS and AT deficiency in 6 patients (7.5%).

Among the 80 patients included, the search for a lupus antibody was made in only 8 patients, revealing an isolated presence of an anticoagulant lupus in two cases.

Among the 50 patients with venous thrombosis, 26 had an inhibitor deficiency (52%). Among the 30 patients with arterial thrombosis, 17 assessments were positive (57%).

4. Discussion

Thrombophilia refers to a set of congenital or acquired molecular abnormalities leading to an increased risk of thrombosis, but it is recognized that a significant proportion of individuals carrying this abnormality will never develop thrombosis. Conversely, in almost half of patients with recurrent thrombotic disease, or even familial, the most thorough biological investigations do not show any abnormalities [7]. The thrombotic pathology concerned is mainly venous (1 to 2 individuals in 1000 each year) [8]. Although less clearly demarcated, hypercoagulability is also suspected to play a role in arterial thrombosis [9].

VTE is a frequent and serious disease due to its silent nature, emphasizing the importance of adequate prophylaxis in favorable settings. The main complication is pulmonary embolism, which has a terrible prognosis. Venous thrombotic accidents and post-thrombotic sequelae represent an important part of public health expenditure [2].

The history of thrombophilia has been and continues to be marked by various discoveries. In 1856 Rudolf Virchow described the triad of major determinants of a VTE

- Blood stasis
- Modification of the vascular wall
- Hypercoagulability.

Hereditary thrombophilia was first described at the beginning of the 20th century, and Egberg was the first to propose this term in 1965 when he had just described the first case of constitutional Antithrombin deficiency.[10].

Other inhibitor deficiencies have subsequently been described. The first protein C (PC) deficiencies were described in 1981 and the first S protein (PS) deficiencies in 1984. In 1993 Dahlback et al described resistance to the anticoagulant activity of activated PC (APCR). Bertina et al showed that this was linked to a point mutation in the factor V gene called

the Leiden mutation, named after the city where it was discovered (Netherlands) [7]. In 1996, POORT identified a new coagulation abnormality associated with a thrombotic tendency: the G 20210 A mutation of the thrombin gene [11].

In 1969, Mcgully suspected the incrimination of homocysteine in thrombogenic phenomena [12]. In the Moroccan context, there is a lack of data concerning VTE at the national level and the declaration is not mandatory, the real prevalence of this pathology is impossible to determine. There are therefore only series compiled by services, especially universities, which do not reflect the actual incidence / prevalence.

In our series, a biological abnormality was diagnosed in 43 patients (53.75%). These results are similar to those of the literature. It is reported that 30-50% of the deficits are present in patients with at least one thrombotic episode [13].

A study reported that 4.4% of Europeans, 7% of Greeks have resistance to PC, while in Africa this anomaly is rare [1].

In a study carried out in Algeria, the resistance of activated protein C was detected in 10 cases among the 124 investigated, so the percentage is 8.1% [14]. Another Tunisian study obtained a percentage of 13.9% [15].

In our study, resistance to activated protein C was noted in 7 patients (8.75%), of which 2 patients had only an APCR, and 5 had other associated abnormalities.

Our result is close to that of the Tunisian and Algerian study, and does not correspond to the literature which considers the APCR as the most frequent risk factor, which leaves the question of a particular Mediterranean profile.

In our study, protein S deficiency was noted in 29 patients (36.25%), 9 of whom had an isolated deficiency, and 20 a deficiency combined with other abnormalities, representing the most common risk factor.

In a study carried out in Algeria, the PS was measured in 108 individuals, the study showed 16 deficits with a percentage of 14.8%. [17]

In a study carried out in Marrakech, the protein S deficiency was the most common of the order of 42% [18].

The study carried out in Algeria and another in Tunisia, show that the deficit in PS is the most frequent [14], [15]. Other studies found 5% in West Germany, 5% in Italy [14].

Our result corresponds to certain data in literature; it is close to that obtained by the studies carried out in Marrakech, Tunisia and Algeria, while noting a large difference with the studies carried out in Germany and Italy.

This may be due to ethnic variability, hence the need for a multicenter study to confirm these results.

Protein C deficiency was noted in 26 patients (32.5%). For 6 patients, this was an isolated PC deficiency, for 20 patients it was a deficiency associated with other abnormalities.

Tunisian study showed 20.1% of patients had PC deficiency [15].

In a study carried out in Algeria, protein C deficiency was sought in 171 patients, 11 cases of deficiency with a percentage of 6.4%.

Other studies found 4% in West Germany, 7.5% in Italy [14].

This difference between our results and the data in the literature may be due to a high percentage of people with CP deficiency in the Moroccan population.

Antithrombin deficiency in 12 patients (15%), 2 of whom had an isolated deficiency, and 10 a deficiency associated with other abnormalities. A study carried out in Algeria, showed an AT deficiency in 18 patients with a percentage of 9.7% [14]. However, a Tunisian study obtained 13.9% of patients with AT deficiency [15].

Our result is consistent with the literature.

Table 2 Breakdown of results according tocombined deficits

Study	PS	PC	AT	APCR
Algeria	14.8%	6.4%	9.7%	8.1%
Tunisia		20.1%	13.9%	13.9%
Marrakech	42%			
West Germany	5%	4%		
Italy	5%	7.5%		
Our study	36.25%	32.5%	15%	8.75%

Sex is not involved in the determinism of thrombophilia. Studies mainly assess the effect of gender on the risk of recurrence [19], [20], in our study, the sex ratio is 0.57

According to the latest recommendations, there is no need to do a thrombophilia assessment in patients over 60 years (GEHT). The concept of thrombophilia is applied to thrombosis occurring before the age of 45 years. In our study, the average age is 32.29 years ranging from 1 year to 79 years, with a predominance of the age group] 30-45 years]. 15% of our patients have an age range] 45-60], explained by the fact that the thrombophilia assessment is requested regardless of age, even in elderly subjects with thrombosis.

In the EPCOT study which looked at the incidence of thromboembolic events in asymptomatic subjects from "thrombophilic" families, the mean age of occurrence of thromboembolic events was 40 years for inhibitor deficits, versus 63 years for the FVL. In a similar methodological approach, the presence of an FVL does not seem to have an impact on the risk of TE event beyond the age of 60.

According to the sources, the risk of VTE is multiplied by 2 after each decade. Beyond 65, the risk increases exponentially [21].

Indeed, this risk is estimated at 1/10000 before the age of 40, at 1/1000 after 40 years and 1/100 beyond 75 years. There is an exponential increase of factor of 1.9 per decade. This would be due to the limitation of mobility

Knowledge of the triggers of VTE is fundamental because it makes it possible to consider adequate anti-thrombotic prophylaxis in subjects with thrombophilia, whether they are symptomatic or not. [22].

An epidemiological study of more than 4,000 patients established that the risk of VTE was arbitrarily set at 1 for a 35-year- old subject, it rose to 2.2 at 50 years and increased considerably afterwards. [23].

Having a history of VTE increases the risk of DVT by 15.6 [24].

Cancer would increase the risk of thrombosis. Activation of coagulation is common in cancerous conditions. On the other hand, the mechanisms of this hypercoagulability are multiple, complex and imperfectly understood. [25].

A small number of studies have clearly shown that the risk of postoperative thromboembolic events is at least twice as high in a patient with cancer [26]. General surgery, in the absence of any prophylaxis, causes thrombosis in 15 to 30% of patients. In the case of a knee or hip prosthesis, under the same conditions, 40 to 70% of patients with thrombosis are found. Gynecological and urological surgeries are also thrombogenic with 30% of cases of proximal DVT [27], [28].

The frequency of thrombosis is high after pelvic trauma or fracture of the femur. This situation would be linked to the passage, in the circulating blood, of the pro-coagulant medullary material, particularly rich in phospholipids, and to the lesions combined with blood stasis. [26].

In 1961, the first case of DVT associated with taking estrogen-progestogen was detected [26]. The combination of oral contraception with the factor V Leiden mutation increases the risk of VTE by a factor of 11, and the association with the 20210A prothrombin mutation by a factor of 7[29], [30].

It is therefore a significant risk in the female population. According to studies, for users of oral contraceptives, this risk is 50 to 70 cases per 100,000 women per year for 2nd Generation pills and 90 to 120 per 100,000 women per year for 3rd Generation pills. [31].

The frequency of thrombosis during pregnancy is 1/1000 therefore the risk of thrombosis is 5 times higher than in the general population, because there is an exacerbation of all elements of the Virchow triad. Pregnancy itself carries a risk of thromboembolism [32].

In women under 40, half of VTEs are believed to be related to pregnancy or postpartum [32].

The prevalence of thrombosis in patients with catheters is between 5 and 66%. The risk factors depend on the site of implantation of the catheter the position of the end of the catheter, the type of material used (silicone or polyurethane), the nature of the drug administered in the catheter (nutrient mixture, chemotherapy modifying the catheter properties), terrain (child, patient condition …) [33].

L-asparaginase (Aspa) has relatively specific therapeutic activity in ALL. As a post-treatment complication, Aspa causes a hypercoagulable state and increases the risk of thrombosis, mainly venous with an incidence of 5 to 10%.

A study has shown a progressive decrease in AT in 214 adults receiving 6 injections of 7,500 IU / m^2 induction [34].

In our study, we noted a predominance of the presence of a malignant pathology as a risk factor, with a number of patients of 7 (17.07%), of which 5 patients had acute lymphoblastic leukemia (ALL), which may be be explained by the post- therapeutic complication induced by L- Asparaginase which predisposes to hypercoagulability by decrease in AT.

The frequency of occult cancer is significantly higher when it is a priori unprovoked VT, without a recognized cause, than when VT occurs after a precipitating factor [35].

However, in another study in Isère, involving 1250 patients who presented a definite episode of VTE, 249 had or will have cancer (20%)[36]. We find a non-negligible proportion of patients with a malignant pathology, which is consistent with the literature.

The clinical presentation of thrombosis is very variable, no clinical sign is sensitive and specific enough to confirm or rule out VTE. Each genetic deficit and each given genetic anomaly results in its own phenotypic expression, which explains this clinical heterogeneity. These anomalies have a more or less significant thrombogenic potential which allows a better understanding of the involvement of partially protective compensating factors and especially the multi-gene interaction of certain thrombophilia in the genesis of thromboembolic accidents [37].

The data from the interview and the clinical history allow for the selection of patients who will undergo the biological assessment for thrombophilia.

Thrombophilia work-up examinations must be carried out in accordance with the analytical recommendations [38].

Data from the literature show that deficits in natural anticoagulant proteins are relatively rare (<0.5% in the general population), but are associated with a more severe thrombophilic tendency, with a 5 to 10-fold increase in risk and a annual incidence of MTEV> 1% [22].

The different thrombotic risks associated with thrombophilic traits interact in different ways with the concomitant conditions acquired for the development of VTE. Thus, a higher prevalence of unprovoked VTE (55% to 60%) is observed in patients with insufficient natural anticoagulants and who frequently present the first thrombotic event before 45 years of age. [22].

5. Conclusion

Thrombophilia, a pathology of relatively recent knowledge, constitutes a multifactorial pathology associated with heterogeneous clinical expression.

The laboratory diagnosis of thrombophilia is easy, but it must be accompanied by clinical information, complete, and controlled, to have a good clinical and biological conclusion.

Finally, prescribing a thrombophilia assessment is simple, but taking care of the patient in the event of an abnormal assessment is something else. It is necessary to explain during a consultation with the patient and often his entourage, the ins and outs of the result, submit the documents, in particular the genetics which is sent only to the prescribing doctor, a Thrombophilia liaison sheet (to be shown for any medical consultation), explain the consequences of anticoagulant treatment, the risk of recurrence of VTE, contraception, pregnancy, children, etc.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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