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AN OVERVIEW ON HEREDITARY AND ACQUIRED HYPERCOAGULABILITY

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AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

A typical definition of hypercoagulability is the predisposition to develop venous thromboembolism due to an underlying hypercoagulable state caused by hereditary or acquired blood coagulation or fibrinolysis problems. Clinical signs of hypercoagulability can be fatal or extremely damaging. About 80% to 90% of patients can have hypercoagulability diseases accurately recognised. Determining the origin of hypercoagulability may influence

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the kind and length of treatment for the accompanying thrombosis. As a result, hypercoagulability is not a single, unified disease process but rather a collection of risk factors that may or may not lead to thrombosis, depending on the severity and number of risk variables as well as environmental exposures. The former includes prothrombotic polymorphisms in the genes encoding for factor V (i.e., factor V Leiden) and prothrombin, as well as shortages of natural anticoagulants such antithrombin, protein C, and protein S. It also includes elevated values of clotting factors (particularly factor VIII). The latter problems mostly include hyperhomocysteinemia, acquired elevations of coagulation factors or acquired reductions of natural inhibitors, malignancy, and antiphospholipid antibody syndrome.

Keywords: Antiphospholipid syndrome; hereditary thrombophilia; risk factors; factor v leiden; thrombophilia; venous thromboembolism.

1. INTRODUCTION

"Hypercoagulability, also known as thrombophilia, is a pathological condition marked by excessive coagulation or coagulation in the absence of bleeding. A thrombus is produced when several blood components interact. Venous thromboses, such as deep vein thrombosis (DVT) and pulmonary embolism, are distinct from arterial thrombosis, which occurs in myocardial infarction and stroke (PE). Venous and arterial thrombosis have different pathophysiology and treatments, although risk factors are similar" [1,2]. In terms of vascular diseases, acute myocardial infarction and stroke are followed by venous thromboembolism (VTE). Deep vein thrombosis (DVT) and pulmonary embolism (PE) are the two main clinical events that characterize it. PE frequently follows DVT to create a distinctive clinical picture. Even though VTE is a widespread condition, the underlying pathogenic mechanisms are only partially understood, especially in compared to those of atherothrombosis [2]. Thrombophilia are hemostatic diseases, classified as hereditary and acquired, which affect about 15% of the Caucasian people who are inclined to thrombotic phenomena. Hereditary conditions include antithrombin III (ATIII) deficiency, proteins C (PC) and S (PS) deficiency, and genetic mutations such as factor V Leiden (FVL), prothrombin gene G20210A (PTM), and the thermolabile form of the methylene tetrahydrofolate reductase (MTHFR) gene C677T. "The most common acquired thrombophilias are caused by antiphospholipid antibodies, that include lupus anticoagulant (LAC) and anticardiolipin antibodies. Thrombophilias resulting from a combination of inherited and acquired components, such as the VIIIc factor, hyperhomocysteinemia, and acquired activated protein C resistance, are identified" [3]. Factor V Leiden testing and prothrombin G20210A mutation analysis are two of the most commonly requested molecular genetic tests in the US (Spector, 2005). Widespread testing has resulted from the realisation that these genetic risk factors are relatively prevalent in people with a history of venous thromboembolism (VTE) and may have implications for therapy, and/or decisions concerning the use of oral contraceptives and pregnancy. Testing is possible in people with a personal or family history of VTE, in pregnant women who have experienced miscarriage or other pregnancy difficulties in the past, and occasionally in people who have had a stroke or myocardial infarction [4].

1.1 Hereditary Thrombophilias

Most frequently, the term "hereditary" or "inherited" thrombophilia has been used to describe diseases where a genetic mutation alters the quantity or function of a protein in the coagulation system. Antithrombin (AT), protein C (PC), and protein S (PS) are three examples of mutations with loss of function [5-7]. Factor V Leiden (FVL) and prothrombin gene 20210 A/G (PGM) mutations are examples of mutations that result in gain of function [8,9]. In a population-based case-control research, the 20210 A allele was shown to be a frequent allele (1.2% allele frequency; 95% confidence interval: 0.5% to 1.8%), which elevated the risk of venous thrombosis by almost three times (odds ratio: 2.8; 95% confidence interval: 1.4 to 5.6). For both sexes and all ages, the risk of thrombosis increased. Prothrombin levels were observed to be higher in people who had the 20210 A allele.

The highest percentile of plasma prothrombin levels (> 1.15 U/mL) is reached by 87% of people with the 20210 A allele. Prothrombin elevation has also been linked to an increased risk of venous thrombosis [9].

1.2 Acquired Thrombophilia

Acquired thrombophilia is linked to higher risk of venous thromboembolism (VTE). The most common form of acquired thrombophilia, known as antiphospholipid syndrome (APS), is linked to both arterial and venous thromboses [10]. The risk of thrombosis can be increased by a variety of acquired circumstances, including acquired abnormalities in coagulation proteins (such as deficiencies in the

natural anticoagulants, activated protein C resistance in the absence of FVL), and certain disorders (e.g. myeloproliferative neoplasms, paroxysmal nocturnal hemoglobinuria, cancer). Some drugs, such as chemotherapy and exogenous hormones, raise the risk of thrombosis. Risk is also increased by acquired traits like smoking, obesity, advancing age, and pregnancy [11].

2. EPIDEMIOLOGY

Venous thromboembolism is the second most common cardiovascular disorder after myocardial infarction; it is more common than stroke. It affects 1 to 5 people out of every 1000 in the general population each year. The incidence increases with age, beginning with 1 per 100000 per year in children and increasing to 1 per 1000 per year in adults and 1/100/year in the elderly. The frequency of thrombophilias associated with APS, APC resistance, and elevated factor VIII was reported to be 25 to 28%; protein C deficiency, protein S deficiency, hyperhomocysteinemia, and prothrombin mutation was reported to be 5 to 10%. Hypercoagulability disorders are responsible for up to 4% of strokes [12]. Neonate purpura fulminans, renal vein thrombosis, vena cava thrombosis, and hepatic vein thrombosis are among the paediatric illnesses connected to inherited thrombophilia. Genetic thrombophilia has been associated to cerebral palsy, Legg-Calve-Perthes disease, and pulmonary embolism [13]. The incidence of newborn purpura fulminans and disseminated intravascular coagulation is somewhere between 1 in 16,000 and 360,000 in homozygous individuals with complete lack of protein C or S [14]. Patients of all ages suffer significantly from thromboembolic events, which result in severe death and morbidity. Neonates have a higher risk of developing thromboembolic issues than older children do, possibly as a result of lower levels of antithrombin, heparin cofactor II, and protein C as well as a decreased fibrinolytic capacity [15]. After the first year of life, the prevalence of vascular accidents considerably declines, with a second rise during puberty and adolescence that is once more correlated with decreased fibrinolytic activity. Over the past 40 years, there has been a molecular understanding of thrombophilias that has increased, and this understanding has changed how the illness is diagnosed and treated. To comprehend the inheritance patterns and hazards for people with inherited thrombophilia, studies have been conducted in a variety of communities. Initially, it was thought that familial thrombosis was an autosomal dominant condition with variable expression and penetrance. The combination of two or more gene abnormalities in a family, according to more recent research, may actually cause congenital thrombophilia [16].

2.1 Genetic Causes of Thrombosis

The initial genetic factors linked to venous thrombosis were deficiencies in protein C, protein S, and antithrombin. Less than 1% of people have any one of these three rare impairments (type I antithrombin deficiency in less than 1 per 1000) [17,18]. In general, these impairments seem to roughly 10-fold increase risk in heterozygotes [19-21]. Most medical professionals believe that antithrombin deficiency poses a greater risk than PC or PS insufficiency. Extremely uncommon homozygous lack of a natural anticoagulant causes a marked thrombotic tendency with extensive thrombosis (purpura fulminans) appearing shortly after birth [22,23].

2.2 Antithrombin III (ATIII) Deficiency

The thrombin-antithrombin (TAT) complex is formed when antithrombin III binds to heparin on endothelial cells and inhibits coagulation. The frequency in the general population could be 1 in 500. Among the inherited thrombophilias, its deficiency provides the highest risk for thrombotic events and might manifest as early age thrombosis (less than 50 years old). Although it is produced in the liver, antithrombin does not require vitamin K. A lack of ATIII might result from decreased synthesis (liver injury) or increased loss (nephrotic syndrome, enteropathy, DIC, sepsis, burn, trauma, microangiopathy, and cardiopulmonary bypass surgery) [24].

2.3 Factor V Leiden

Factor V Leiden (factor V R506Q), the most prevalent genetic disorder among Caucasians that predisposes to thrombosis, with a carrier prevalence of about 5% [25,26]. The action of activated protein C in the breakdown of factors Va and VIIIa is also assumed to be supported by factor V, protein S, and other cofactors. As a result, the anticoagulant activity of activated protein C is reduced when this cleavage product is absent [27]. Patients with a history of thrombosis have been found to have a number of mutations at the factor V Arg306 residue. On rare occasions, patients with type I factor V deficiency and the factor V Leiden mutation have been reported to have heterozygous APC resistance [28]. A mutation at one of the locations in factor V where APC cleaves factor V results in this intermediate phenotype [18]. Vein thrombosis risk increases by 3- to 8-fold in heterozygous carriers of factor V Leiden and by 50- to 80-fold in homozygous carriers [29,30].

2.4 Protein C Deficiency

Heterozygous protein C deficiency affects 5-9% of individuals with a history of VTE [31] and 0.14-1.5% of the general population [19] An elevated risk of 2-

to 11-fold for VTE exists in people who are heterozygous for protein C deficiency [32]. Protein C insufficiency, as opposed to AT deficiency, may also be linked to an increased risk of arterial thrombosis in those under the age of 55 [33]. The majority of people who have an inherited protein C deficiency are heterozygotes for the PROC gene mutation and have a modest deficiency that is inherited in an autosomal-dominant manner. Protein C levels in subjects with heterozygous protein C deficiency are typically between 35 and 65% of normal, while values as high as 68% have been noted in "deficient" people [34]. In addition to purpura fulminans and disseminated intravascular coagulation (DIC) in the newborn phase, homozygous protein C deficiency manifests as substantially reduced protein C levels [35]. The two main subtypes of protein C deficiency are as follows. The most prevalent type of protein C deficit is type I, which is marked by a quantitative lack of the substance, as opposed to type II, which is marked by a qualitative lack of protein C (but frequently a quantitative one). There is a higher prothrombotic risk for both types [36].

2.5 Protein S Deficiency

By the time they are 60 years old, one-third of PSd patients will have venous thrombosis [37-39]. Homozygotes for the defect can develop purpura fulminans, which is characterised by severe, widespread systemic thrombosis and associated tissue necrosis [40-42]. Warfarin-induced skin necrosis has also been reported in PSd patients and is connected to variations in the production and turnover [43].

2.6 Prothrombin 20210A

About 3% of Caucasians have this mutation (PT20210A, which changes position 20210 of prothrombin from G to A), with regional variations in occurrence ranging from 1% to 6% [44,45]. This mutation is detected in 6% of venous thrombosis patients who participated in the Leiden Thrombophilia Study [44]. It appears to be mediated by higher prothrombin levels as it roughly triples the risk of thrombosis [44].

2.7 Acquired Causes of Thrombosis

2.7.1 Antiphospholipid antibodies

The antiphospholipid antibody syndrome (APS) is a systemic, acquired, immune-mediated disease marked by the ongoing existence of autoantibodies targeted targeting phospholipid and protein-containing molecular complexes. Although it is still largely unclear, the prevalence of APS is thought to range between 2 and 4 percent in the general population [46]. Antiphospholipid antibodies enhance the risk of thrombosis in individuals, whether they have isolated antiphospholipid antibodies or systemic lupus erythematosus (SLE), which has these antibodies in 50% of cases. Each patient has a unique clinical presentation and thrombosis risk. Overall, the danger has grown by nearly ten times [47-49].

2.7.2 Cancer

According to reports, cancer patients have a higher risk of thrombosis; however, this risk mostly depends on the kind of cancer, its stage and histology, as well as the therapeutic measures (e.g., surgery, chemotherapy, radiotherapy) [36]. The link between cancer and hemostasis is fundamentally bidirectional, and the pathophysiology of thrombosis in cancer is complicated [50,51]. Blood stasis, endothelial damage, and hypercoagulability make up the pathophysiology, which is mostly connected to deviations from Virchow's triad [52].

2.7.3 Surgery

Depending on the type of surgery, up to 50% of patients will develop thrombosis without thromboprophylaxis [53,54]. The risk of thrombosis during orthopaedic surgery on the hip and knee ranges from 30% to 50%. Additionally risky are abdominal surgeries (up to 30%), gynecologic surgeries, and urologic surgeries (in particular, radical prostatectomy) [55]. Due to the widespread use of anticoagulant prophylaxis, these substantial risks are no longer present [36].

2.7.4 Immobilization

Thrombosis can happen in a variety of situations that involve immobility, including paralysis, bed rest, plaster casts, and extended travel [56-58]. The risks, causes, and prevention of travel-related thrombosis are the subject of numerous investigations. In these studies, hypoxia and hypobaria, which have been shown to activate coagulation [59], will also be examined.

2.7.5 Hormonal replacement therapy

Recent research has shown that hormonal replacement therapy (HRT) is linked to a 2- to 4-fold increased risk of thrombosis [60-62].

2.7.6 Pregnancy

Approximately 1 in 2000 pregnant women will get thrombosis. Additionally, there is a higher risk during

puerperium than during pregnancy, according to the majority of research. The long antepartum period of heparin injectable therapy and the availability of oral anticoagulation post-partum all contribute to the higher prevalence of anticoagulant prophylactic prescriptions postpartum than throughout pregnancy [63].

2.7.7 Oral contraceptives

Numerous studies have shown that oral contraceptives, especially the low-dose oral contraceptives now in use, roughly quadruple the risk of thrombosis [64-66]. An oestrogen and a progestogen are typically found in oral contraceptives. The amount of ethinylestradiol in the oestrogen dose has decreased through time from 100 mg or more to contemporary formulations with 30 mg or less. There is no convincing evidence that this has reduced risk, as both the earliest and most recent studies reveal 4- to 8-fold increases in risk for oral contraceptive users [64,67]. More than ten studies have demonstrated that the presence of third-generation progestogens, such as desogestrel and gestodene, in oral contraceptives increases the risk of venous thrombosis by twofold compared to formulations that only contain levonorgestrel. Progestogen content may also affect thrombotic risk (so-called second-generation progestogen) [64-70].

3. DIAGNOSIS

Differentiating between provoked and unprovoked thrombosis by history and physical is crucial for the investigation of patients experiencing thrombotic episodes. Different circumstances allow for the observation of thrombotic events. Therefore, it is crucial to establish a broad differential diagnosis that takes into account both the more common (mobility, travel) and less common entities, such as cardiac disease (atrial fibrillation, cardiomyopathy, mitral valve prolapse, prosthetic valves), non-bacterial thrombotic endocarditis (NBTE), and hematologic causes like disseminated intravascular coagulopathy (DIC) and heparin-induced thrombocytopenia (HIT) [71,72]. Diagnostic workup can be guided by clinical decision aids like the HIT score, which can assist in assessing pretest probability. Vaso-occlusive events should have thrombophilia on the differential diagnosis list. Thrombophilia can be connected to arterial thrombosis, including osteonecrosis, ischemic stroke, and myocardial infarction [73-76]. Myocardial infarction in young people was caused by known cardiovascular risk factors rather than thrombophilias [77]. According to certain research, myocardial infarction with non-occlusive coronary arteries should be diagnosed with thrombophilia (MINOCA) [78,79]. Venous thromboembolism caused by a patent foramen ovale may potentially link thrombophilias to stroke in young persons [80].

4. MANAGEMENT

Understanding the biology of the disease, its prevalence, the associated morbidity and mortality, and the available therapy choices can help in treating inherited and acquired thrombophilic disorders. Hyperhomocyst(e)inemia and activated protein C (APC) resistance are caused by genetic alterations, which have been discovered. Disorders that can be inherited or acquired include antithrombin deficiency, protein C and protein S deficits, and plasminogen deficiency. Trousseau's syndrome, myeloproliferative syndromes, and antiphospholipid antibodies are acquired conditions. All thrombophilic illnesses receive the same or a comparable course of treatment for acute arterial thrombosis or venous thromboembolism. The risk of a main or recurring acute thrombotic event is taken into account when determining long-term management, together with the risk of the suggested medication. The danger of the recommended treatment should be carefully considered when long-term anticoagulation is suggested. Warfarin's use is constrained by its bleeding risk, uncertain efficacy, and cutaneous necrosis risk. Fixed low-dose unfractionated porcine heparin and low-molecular-weight heparins (LMWH) offer important benefits for long-term therapy [81]. Treatment for VTE is divided into three phases: acute (within a few days of the incident), intermediate (within three months of short-term anticoagulation), and chronic (long-term anticoagulation for more than 3 months) [82]. Age, proximal versus distal deep vein thrombosis having a larger thrombotic burden, elevated d-dimer, and spontaneous VTE all contribute to a higher recurrence rate and can result in prolonged coagulation [83]. To stop recurrent VTE, many anticoagulants and antiplatelets are available [84]. These include dabigatran (RE-MEDY and RE-SONATE trials), rivaroxaban (EINSTEIN trial), vitamin K antagonist (VKA), aspirin (as evaluated in the WARFASA and ASPIRE trials), and apixaban (AMPLIFY trial) [85].

5. CONCLUSION

Venous thrombotic events are the result of numerous, intricate interactions between inherited and acquired variables. Patients with venous thrombosis frequently have congenital thrombophilic diseases. In fact, thorough understanding of each potential risk factor's role in the pathophysiology of venous thrombosis is necessary to aid in a quicker and more accurate diagnosis of these conditions, as well as to make it

easier to treat patients who already have symptoms and prophylaxis patients who are at higher risk. Therefore, it is preferable to prevent DVT in high-risk populations than to treat the illness and its sequelae after an acute occurrence.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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