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Risk Factors for Chronic Thromboembolic Pulmonary Hypertension – A Review

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Abstract: ***Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of pulmonary hypertension caused by obstruction and vascular remodeling of pulmonary arteries following Pulmonary Embolism, which leads to increased pulmonary pressure and right ventricular failure. Several studies have reported that the incidence of the disease is between 0.1% and 9.1%. However, since many patients with CTEPH do not refer to have suffered an acute Pulmonary Embolism (PE), the true incidence of the disease is believed to be higher. Risk factors that predispose the development of CTEPH include: the initial size of thrombus and numerous associated host co morbidities. Homeostatic risk factors include: the level of plasma factor VIII and antiphospholipid antibodiesor intrinsic abnormalities in fibrinogen. Co morbidities include: splenectomy, ventriculo-atrial shunts, infected pacemakers, blood groups other than 0, chronic inflammatory diseases such as osteomyelitis and inflammatory bowel disease, antiphospholipid antibodies, thyroid replacement therapy and a history of malignancy. The prognosis of this disease is poor,if left untreated. In symptomatic patients with surgically accessible CTEPH, the treatment of choice is pulmonary endarterectomy (PEA), but up to 40% of patients evaluated for PEA may be denied surgery for different reasons, including the presence of significant concomitant small-vessel disease. The aim of this article is to highlight the homeostatic factors and clinical conditions that increase the risk for CTEPH.***

Keywords: chronic thromboembolic pulmonary disease (CTEPH), acute Pulmonary Embolism (PE), risk factors

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a special form of pulmonary arterial hypertension, in terms of, not only, the still unknown incidence of this disease, but also poor prognosis despite the fact that theoretically it can be totally curable by pulmonary endarterectomy (PEA)[1], [2]. Late and misdiagnosed of CTEPH, as well as the mistreatment of this disease as pulmonary arterial hypertension (PAH), leads to delays in referral of patients for PEA, which result inincreased mortality in this category of patients. In this context, a better understanding of risk factors which lead to the development of CTEPH could improve early diagnosis and appropriate treatment, thereby, limiting disease progression and improving survival.

2. Risk Factors for Cteph

2.1 Acute pulmonary embolism

Nowadays it is widely accepted that the main cause of chronic thromboembolic pulmonary hypertension is acute pulmonary embolism. The risk of development CTEPH after an acute episode of pulmonary embolism is directly influenced by several factors including: the pulmonary artery pressure (PSAP) > 50mmHg at the time of presentation, previous or recurrent deep venous thrombosis, large perfusion defects and idiopathic PE. In recent studies, it is being observed that approximately 70% of patients with CTEPH had a history of venous thrombosis versus only 11% of patients who had PH without thromboembolic etiology [3].

2.2 Homeostatic risk factor

2.2.1 Thrombophilic factors

Specific risk factors for venous thromboembolism have been identified also as risk factors for CTEPH. Traditional risk factors for VTE include antithrombin deficiency, protein C deficiency, protein S deficiency, factor V Leiden, plasminogen deficiency, and anticardiolipin antibodies. However, numerous studies have highlighted a difference in regards to the factors implicating thrombophilia leading to the development of chronic thromboembolic pulmonary hypertension: hyperhomocysteinemia, high level of PCR, fibrinogen and Factor VIII, increase the risk for systemic arterial thrombosis in this category of patients [4]. Factor VIII is the first prothrombotic factor for whichexists clinical evidence regarding its correlation with CTEPH. The number of patients with high plasma level of factor VIII and Von Willebrand was highly increased between those with CTEPH compared to patients with Pulmonary Arterial Hypertension. After pulmonary embolism has occurred, these factors contribute to the further formation of in situ thrombosis. The increased production of Factor VIII is associated with TVTH deep vein thrombosis and recurrent pulmonary embolism [5]. Factor VIII activates the factor X, which together with factor V Leiden cause the transformation of thrombin from prothrombin. In CTEPH, it is observed that the level of factor VIII is increased and it remains unchanged even after successful thrombendarterectomy [6].

2.2.2 Non –"0" Blood Group

An interesting study, recently published, has highlighted the fact that CTEPH is more frequent between individuals with non-"0" blood group (which reflect an oligosaharide structure defined genetically and lipoproteins (LpA) [7]. It has been found that 77% of patients with CTEPH had a non- "O" blood group compared with 58% of patients with PAH. [7]. High levels of lipoprotein A which affects hypercoagulability, are noticed in CTEPH compared to control groups with PAH and healthy controls [8]. And this evidence implicates the role of fibrinolysis in this pathology.

2.2.3 Markers of inflammation

It is demonstrated through numerous studies that the presence of inflammation in patients who develop chronic thromboembolic pulmonary hypertension is responsible for pulmonary vascular remodeling leading to rapid worsening of the disease and directly influencing prognosis [9]. Markers of inflammation are increased in patients with CTEPH as compared with healthy controls group. Infiltration of the inflammatory cells is discovered in proximal pulmonary arteries of CTEPH patients suggesting the inflammatory role in the progression of the disease [9].

(a)Fibrinogen

There are noticeable anomalies in the structure and function of fibrinogen in CTEPH patients compared to healthy controls [10]. Fibrinogen plays a very important role balancing the homeostasis by interacting in coagulation and fibrinolysis. Itsprothrombotic anomalies in CTEPH explain the persistence of thrombus after an acute Pulmonary Embolism. An important connection is found between the carriers of polymorphism of fibrinogen AαThr312Ala in CTEPH patients compared to healthy controls. This polymorphism alters the structure of fibrin and predisposes clot fragmentation and embolization. This phenomenon is seen more often in CTEPH patients compared with healthy control group [11].

(b) CReactiveprotein (CRP)

Endothelium is a layer of cells that lines the interior surface of blood vessels. These cells serve as a protective barrier between blood and surrounding tissue and act like a sieve that allows the passage of macromolecules and blood gases from the blood to tissue and controversially [12].Endothelial cell dysfunction, break this barrier, leading in vasoconstriction, adherence of leukocyte, activation of platelet, thrombosis, inflammation and atherosclerosis. It is already known that CRP affect endothelial dysfunction through stimulation of locally vasoconstriction, proliferative and pro-thrombotic properties and the inflammatory molecules in the arteries, factors which participate in the pathogenesis of CTEPH [12]. Increased levels of CRP in CTEPH patients contribute in the activation of the endothelium resulting in: 1) promoting adhesion of the intracellular molecules in the surface of the endothelium, 2) absorption of circulative monocytes, 3) secretion of factor von Willebrand and 4) secretion of endothelin, which may encourage the proliferation of smooth muscle cells. In addition, different studies have highlighted that high level of CPR in CTEPH patients will decline sharply 12 months after thrombendarterectomy [13]. Inside of the walls of the vessels, proliferation of smooth muscle can be stimulated by the production of CRP produced by the smooth muscle cells. In the above context, it is expected that the high levels of CRP predict a bad prognosis of the disease.

2.3Diseases that increase the risk for CTEPH

There are numerous studies that have analyzed the identification of risk factors for the development of chronic thromboembolic pulmonary hypertension, among them; there is a recent study, which has documented the incidence of CTEPH after acute pulmonary embolism excluding patients with previous deep vein thrombosis [14]. This study has reported an incidence of symptomatic CTEPH 3.8% in 2 years after a symptomatic episode of acute pulmonary embolism. The risk factors for developing CTEPH of patients included inthe study were: idiopathic presentation, recurrent episodes and large perfusion defects. The drawback of this study was the lack of previous exclusion CTEPH. It is seen that systolic pulmonary artery pressure > 50mmHg in ages over 70 years old makes the diagnosis of CTEPH more likely after an episode of acute pulmonary embolism [15].

Between 1992 and 2003 another prospective study was conducted in patients with CTEPH comparing with those with non CTEPH after an episode of acute Pulmonary Embolism [16]. Among risk factors and independent predictor of CTEPH were observed: splenectomy as an independent factor of risk, ventrikulo-atrial shunt, infected pacemaker and chronic inflammatory diseases such as osteomyelitis and inflammatory bowel disease. It was noted that about 10% of patients with CTEPH had an associated chronic inflammatory disease compared with patients of the group that did not develop CTEPH after an acute episode TEP [17].

2.3.1 Splenectomy

Splenectomyis known as a risk factor for CTEPH. A study showed that about 5.5% of patients with CTEPH have committed splenectomy in the past, compared with the group of patients with non thromboembolic pulmonary hypertension [3]. Later in time, another subsequent 10 years retrospective study showed that the duration of time from splenectomy until the presentation of CTEPH was 16 years with distal placement of the disease [19]. It is believed that the development of the disease has occurred due to aprocoagulation condition in patients post splenectomy. Prothrombotic condition can be linked to the loss of filtering function of the spleen, where the abnormal red blood cells remain in the peripheral circulation, leading to activation of the coagulation process and consequently the formation of thrombus [20]. From another point of view, we may say thatthrombocytosis due to splecentomy has an incidence of 75% - 82% and can result alone in a state of hypercoagulability and thrombosis. However, thrombocytosis was not found to be strongly associated with the increased risk for CTEPH in a recent study [17].

2.3.2 The antiphospholipidic syndrome

The antiphospholipidic syndrome is an autoimmune disease that causes a hypercoagulation condition through antibodies against phospholipids. It is hypothesized that there is a defect in cell apoptosis, which exposes the phospholipidicmembrane to various plasmatic proteins such as beta-2 glycoprotein I. This protein-phospholipids complex becomes the target of autoanticorps. Also recognized are other hypercoagulate mechanisms of antiphospholipid antibodies which do not depend on beta-2 glycoprotein I, and which include: 1) production of antibodies against the coagulation factors, including prothrombin, protein C and protein S; 2) Activation of the platelets which raise endothelial adhesion; 3) Activation of vascular endothelium, which facilitates the connection of platelets and monocytes. Clinically, this condition of hipercoagulability leads to recurrent arterial or venous thrombosis that can affect any organ. In a study

conducted among patients with CTEPH, antiphospholipidic antibodies were found to have increased compared to the patients with Pulmonary Arterial Hypertension [21].

2.3.3 Therapy with thyroid replacement hormones

It is noted that about 20% of patients with CTEPH are treated with thyroid hormone replacement therapy versus 3.5% of patients with nonthrombotic pulmonary hypertension [3]. Patients with hypothyroidism represent a high risk of thrombosis [22], on the other hand, treatment with levothyroxine increased von Willebrand factor levels [23]. Therefore, it is not quite sure whether the increased incidence of hypothyroidism in patients with CTEPH is due to their own illness, treatment, or both.

2.3.4 Malignant diseases

Venous thrombosis is a common complication of malignant diseases. These patients also have a high risk for recurrent thromboembolic episodes. Malignancy is associated with hypercoagulability due to the release of the inflammatory cytokines, activation of the fibrinolytic system, reduced level of natural anticoagulants and injured fibrinolysis [24]. Statistical studies show that the risk of deep vein thrombosis depends not only on the type of cancer, and the stage of advanced disease, but also advance age, surgery, use of central venous catheters, immobilization and other associated diseases that increase the risk of venous thrombosis as well as for any other patient without malignancy [25], [26]. Most frequent malignancies which cause thrombosis are those of pancreas, ovarian, testicular, brain (since these undergo an invasive neurosurgical procedure), breast, colon, lung, renal and thyroid. Data indicates that the presence of canceralone, increases the risk for thrombosis 4.1 times, while chemotherapy increases the risk of thrombosis to 6.5 times [27]. Pulmonary arteries can be obstructed by thrombus, necrotic separated cells or direct extension of the tumor into the cava vein and right heart chambers. For this reason, it is evident that patients with cancer have a higher risk for CTEPH compared to those with non-thromboembolic pulmonary hypertension (12.2% vs. 4.3%) [3].

3. Conclusion

Based on our analysis, some of the risk factors which predispose development of CTEPH are already known. Among the most important factors, we wish to emphasize, areacute Pulmonary Embolism, splenectomy, chronic inflammatory diseases and abnormal pro coagulate proteins. Research supports the factthat plasmatic factors (hypercoagulation, blood group and the number of platelets) and abnormal vascular remodelation process (associated with inflammatory conditions) contributes to obstructive disease of big and small arteries. Levels of Factor VIII and Antiphospholipid antibodies are found in higher levels in patients with CTEPH, which are factors that lead to the formation of in situ thrombosis, which also plays an important role in the pathogenesis of CTEPH and in the organization of abnormal function of endothelium after a thromboembolic episode.

Despite numerous studies that are aimed at the diagnosis and treatment in the early stages of the disease, the prognosis of patients with chronic thromboembolic pulmonary hypertension is poor, because more than one-third of the patients at the time of diagnosis cannot be treated optimally. In this context, a better understanding of risk factors which lead to the development of CTEPH could improve early diagnosis and appropriate treatment, thereby, limiting disease progression and improving survival.

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