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Genetic Regulations of Thrombosis

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ABSTRACT

Keywords: Venous Thromboembolism; Deep Vein Thrombosis; Lipoprotein (A); Kringle Domain; ESUS; CELA2A; PCKS9

Abbreviations: Lp(a): Lipoprotein a; PFO: Patent Foramen Ovale; DVT: Deep Vein Thrombosis; CAD: Coronary Artery Diseases; DALYs: Disability-Adjusted Life Years; ESUE: 3.2 Embolic Stroke of Undetermined Source; LDLS: Low-Density Lipoproteins; Apo(a): Apolipoprotein(a); MetS: Metabolic Syndrome; KIV-2: Kringle IV type 2; PAI-1: Plasminogen Activator Inhibitor-1; PCSK 9: Proprotein Convertase Subtilisin/ Kexin Type 9

Introduction

Case Example of an African American Male with Elevated Lipoprotein a (Lp(a))

A 33-year-old African American male was admitted with angina at rest and left sided weakness. Initial EKG in the emergency room showed ST elevation that spontaneously resolved, and patient became chest pain free. Patient immediately underwent cardiac catheterization, which showed no obstructive lesion. A brain MRI/MRA showed multiple lesions suggestive of an embolic event. Patient's hemiparesis improved over 1 week but did not fully resolve. Further workup revealed a Patent Foramen Ovale (PFO) by a transesophageal echocardiogram. His hypercoagulable workup, genetic panel for hypercoagulable state and other blood workups were all negative except for Lp(a) of 311 mg/dL (Normal <50 mg/dL). Thromboembolic events affect both venous and arterial systems with Venous Thromboembolism (VTE) being more common [1]. 1 in every 1000 people in the US population is afflicted with VTE, a blanket term comprising Deep Vein Thrombosis (DVT) and pulmonary embolism [2].

VTE is the third most common acute cardiovascular cause of death after Coronary Artery Diseases (CAD) and ischemic stroke, with DVT being the main cause of loss of 'Disability-Adjusted Life Years' (DALYs) in low and medium income countries and the second major cause in high-income countries [3,4]. Virchow's Triad enumerates three factors that predispose an individual to develop venous thrombosis which include: hypercoagulability, stasis and endothelial injury. By definition, VTE is the result of an elevated hemostatic response giving rise to the creation of a blood clot that hinders blood flow in venous circulation [3]. Genetics, environmental, racial and behavioral factors contribute to the risk of VTE [4]. Many genetic factors that alter structure or function of lipoproteins, glycoproteins, cytokines and chemokines are implicated and well-studied in the propagation of VTE [3,4]. Multiple studies have shown a higher incidence of DVT in African Americans than Caucasians and significantly lower rates in the Asian population [4]. Metabolic Syndrome (MetS) comprising of abdominal obesity, impaired glucose metabolism, dyslipidemia, and hypertension, is concomitant with a procoagulant and hypofibrinolytic state and is associated with increased risk for DVT [5].

Embolic Stroke of Undetermined Source (ESUS) in Patent Foramen Ovale (PFO) Context

ESUS, a subset of cryptogenic stroke, is a term given for a nonlacunar embolic stroke when cardiac and vascular causes of an embolism have been ruled out and no known etiology is found. ESUS accounts for nearly one-third of all ischemic strokes with a high prevalence in young adults. PFO is the most common congenital cardiac abnormality, present in 25% of the population. In patients

with PFO, in situ thrombus formation with emphasis on paradoxical embolization has been rendered as mechanisms of stroke [6]. Patients with PFO had reduced recurrence of cryptogenic strokes after PFO closure [7]. Interestingly, a study done by Wilmshurst and colleagues was the first to show that migraine with aura was improved following PFO closure [8].

Lipoprotein a – Lp(a)

Lp(a) is an independent risk factor for Cardio Vascular Disease (CVD). It is a constituent of the plasma lipid profile, a cholesterol rich molecule comprising of Low-Density Lipoproteins (LDLs) and Apolipoprotein(a) (Apo(a)). The Apo(a) gene is located adjacent to and is structurally similar to the plasminogen gene. Lp(a) demonstrates thrombogenic and atherogenic activity affecting the endothelium via its effect on coagulation, inflammation, as well as vasodilation and vasoconstriction properties of the endothelium. These functions can be explained by its similarity to plasminogen [9]. Apo(a) cDNA contains ten autonomous Kringle domains together with regions similar to the Kringle V and protease domains of Plasminogen. Kringle IV type 2 (KIV-2) is thought to be the most important repeat as the Apo(a) protein produced by KIV-2 manipulates fibrinolysis and thus thrombosis [10]. Lp(a) facilitates thrombogenesis through several paths: platelet aggregation and activation, tissue factor pathway inhibitor (TFPI) inhibition, increased Plasminogen Activator Inhibitor-1 (PAI-1) expression and reduced plasmin production [9].

At high levels of Lp(a), fibrinolysis is disrupted and thrombosis promoted facilitating VTE [10]. A concentration of Lp(a) >50mg/dL poses an increased risk of CVD and is genetically determined but does not fluctuate throughout life [9,11]. Differences in concentrations exist within races due to factors such as polymorphisms [9]. Africans have 2-3 fold higher levels than Europeans [12]. It has been also shown that recurrent vascular events are prevalent in patients with elevated Lp(a) levels after their first ischemic stroke [13]. In 1990, Pauling and Rath found a significant relationship of Lp(a) and ascorbate (vitamin C) which stated that species that could not produce ascorbate had detectable levels of Lp(a). Chronic vitamin C deficiency drastically compromises collagen deposition and produces a plaque morphology that can easily rupture [14]. Thus, the two are inversely correlated in wound healing, atherosclerosis and other disease conditions [12]. Vitamin C is vital for collagen formation and Lp(a) aids wound healing, reduces bleeding and helps vessel wall stabilization. In the absence of Vitamin C, this would explain the physiological function of Lp(a) [15].

CELA2A

A screening for CELA2A targets, a protein encoded by a gene associated with myocardial infarction in humans and enhanced platelet activation in vitro, identified integrin A2B, which binds to integrin beta-3 to form the Glycoprotein (GPIIb/IIIa) receptor complex. Once soluble fibrinogen is bound to GPIIb/IIIa, platelet aggregation-activation is triggered by the receptor complex. Findings of this study suggested that WT-CELA2A binds to and cleaves Integrin alpha-IIb (ITGA2B), thus reducing platelet activation. However, mutant CELA2A stimulates platelet hyperactivation and aggregation. Connections between CELA2A mutations and early onset CAD were also shown in the same study [16]. Thromboprophylaxis is mandatory in all major surgeries to manage a hypercoagulable state which causes high quantities of coagulation factors with the greatest effect produced by factor VIII. Spontaneous thrombotic events, devoid of any causal risk factors, are also prevalent. "Factor V Leiden paradox," states recurrent thrombosis occurs in males yet first thrombosis occurrence is more prevalent in females [4]. Many other genetic factors contribute to VTE. Deficiencies in the natural anticoagulants protein C, protein S and antithrombin increase the risk of DVT 10-fold or more. Non-O blood group, factor V Leiden, prothrombin 20210A and fibrinogen gamma' 10034T are other group of genetic variants that increase the risk by only 2-5-fold. Interestingly, single nucleotide variants in serpin peptidase inhibitor, clade C member 1 (SERPINC1), F11 gene, Glycoprotein 6 gene and a few other genes with unknown function such as HIVEP1, TSPAN15, SLC44A2, ORM1 have shown to collectively increase the risk of DVT by about 50%. Acquired risk factors for DVT include malignancy and surgery as the two main causes with over a 50-fold increase in risk [4,17].

Future Directions

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitors are serine proteases that reduce LDL receptors [18]. Lp(a) apheresis and PCSK9 decrease the plasma Lp(a) by nearly 20%-30%. The question remains whether PCSK9 actually improves the overall outcome of the patient. Novel apo(a) antisense oligonucleotide therapy targeting apo(a) is a promising new progression in therapeutics with more than 90% plasma Lp(a) reduction, awaiting further clinical trials to be established [19].

Conclusion

Lp(a) is independently linked to increased risk of ischemic heart disease, atherosclerosis, thrombosis and stroke. Plasma levels of Lp(a) are influenced by genetic factors [20]. Roughly 20% of the population have elevated levels of Lp(a) [12]. Mechanisms of stroke in PFO patients are known to have in-situ thrombus formation as a causal factor [7]. Associations with CELA2A mutations and CAD show a promising future to possible therapeutic interventions [16]. With several therapeutic methods undergoing clinical trials, there is growing enthusiasm for development of far more efficient therapeutics to combat this global burden.

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