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Genetics of myocardial infarction: The role of thrombosis-associated genes. A review article

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ABSTRACT

Myocardial infarction (MI) is the death of myocytes due to prolonged ischemia which is the result of perfusion-demand mismatch in the corresponding tissues. Although the medical field has progressed tremendously in elaborating treatments in the form of drug-eluting stents and medications, coronary heart disease (CHD) is still the leading cause of death worldwide. In fact, the WHO fact sheet reviewed in June 2016 declares that cardiovascular disease (CVD) is the number one cause of death globally. Therefore, more emphasis should be put on implementing preventive measures to reduce the burden of CHD. Elucidating the details of the genetic predisposition to CHD including MI enhances our prognostic capacities and allows for more effective interventions.

In this review, we explore the contribution of 10 genes to myocardial infarction; these genes code for Factor V, Factor II, MTHFR, PAI, HPA-1, ACE, Apo B, Apo E, Fibrinogen, and Factor XIII. Some of these genes are directly associated with MI. Other genes are less important. The findings are summarized in a table at the end of the review. The take-home message is a recommendation for incorporating genetic screening for the major thrombosis-associated genes (mutations and polymorphisms) into the initial diagnostic work-up of a patient presenting with myocardial infarction or coronary artery disease and into the prognostic and preventive work-up of high risk individuals.

Introduction

Myocardial infarction is the death of myocytes due to prolonged ischemia which is the result of perfusion-demand mismatch in the corresponding tissues. This ischemia is usually the result of a thrombotic occlusion of coronary arteries due to a ruptured atherosclerotic plaque followed by a coagulation process (Alizadeh et al., 2016). Symptoms associated with myocardial infarction usually last for > 20 min, although in some cases less, and in other cases no symptoms are associated with myocardial necrosis. The symptoms are usually chest discomfort with pain radiating to the left arm, shoulder, back, or jaw. The pain is not usually sharp or localizing, and in some cases is associated with shortness of breath, sweating, vomiting, or light-headedness (Alpert et al., 2000). In some atypical cases, discomfort may occur in the epigastrium, shoulder, arm, wrist, or back in the absence of chest discomfort (Alpert et al., 2000). The following table taken from a consensus document of The Joint European Society of Cardiology/American College of Cardiology committee summarizes the different aspects of myocardial infarction;

Pathology	Myocardial cell death
Biochemistry	Markers of myocardial cell death recovered from blood samples
Electrocardiography	Evidence of myocardial ischemia (ST-T segment changes)
	Evidence of loss of electrically functioning cardiac tissue (Q waves)
Imaging	Reduction or loss of tissue perfusion
	Cardiac wall motion abnormalities

Aspects of MI by different techniques (Alpert et al., 2000).

The WHO fact sheet reviewed in June 2016 declares that cardiovascular disease (CVD) is the number one cause of death globally. Moreover, WHO estimates that in 2012, 17.5 million people died from CVD, and 7.4 million of those died from coronary heart disease (CHD) (see link http://www.who.int/mediacentre/factsheets/fs317/en/). Myocardial infarction is a key constituent of the cardiovascular diseases, the burden of which is increasing with the increase in life

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expectancy (Roger, 2007). In fact it is reported in the literature that few years ago, the annual mortality from MI was around 157,000 in the US and around 50,000 in Japan (Yamada et al., 2008). These statistics highlight the need for more effective interventions to reduce the public burden of CHD including myocardial infarction. Identifying the risk factors for myocardial infarction is the first step toward better intervention.

Risk factors for myocardial infarction are usually split into modifiable and non-modifiable. The modifiable risk factors include hypertension, hypercholesterolemia, smoking, diabetes, obesity, increased alcohol consumption, decreased physical activity, anxiety, and depression. The non-modifiable risk factors include older age, male gender, and family history of premature coronary artery disease (Tabei et al., 2014). In fact it is mentioned in the literature that individuals who have a first degree relative with MI are at a seven-fold higher risk of MI than those who do not (Ranthe et al., 2015).

The presence of family history of premature coronary artery disease (CAD) as a risk factor highlights the genetic contribution to the pathogenesis of CAD and MI. In fact, a study conducted in Kuwaiti population in 2009 found a significant association ($p < 0.001$) with an adjusted odds ratio of 9.32 for family history of coronary artery disease and myocardial infarction. The study included 88 MI patients and 122 controls matched for gender and age (Al-Bustan et al., 2009). This high odds ratio sheds light on the genetic contribution to myocardial infarction. In fact, several studies have reported that conventional risk factors contribute only 50% of the total risk of cardiovascular diseases, while the genetic predispositions contribute to the remaining. This genetic contribution may be in the form of polymorphisms or mutations at the level of coagulation cascades, blood pressure regulatory mechanisms, lipid, glucose or homocysteine metabolism (Alizadeh et al., 2016).

Although the medical field has progressed tremendously in elaborating treatments in the form of drug-eluting stents and medications, CHD is still the leading cause of death worldwide. For that, prevention should be emphasized as a strategy to reduce the CHD burden. The success of this strategy depends majorly on the ability to effectively predict disease occurrence in certain patients. This is why more studies are needed to elucidate the details of the genetic predisposition to CHD including MI. This would allow for better prediction, and more effective intervention.

In this review, we explore the contribution of 10 genes to myocardial infarction; these genes code for Factor V, factor II, MTHFR, PAI, HPA-1, ACE, Apo B, Apo E, Fibrinogen, and Factor XIII. We particularly chose these genes because the physiologic interactions of the corresponding mutations/polymorphisms theoretically predispose to a hyper-coagulable state, their association with MI is commonly investigated in the literature, and we have simple tools to screen for them.

Methods

The main source of the studies reviewed is PUBMED. Meta-analysis studies were of specific importance when searching the literature because they provide large samples unlike the limited samples of the majority of the case control studies published in the literature. Review articles were best used to reach possible explanations for the discrepancy in the results among the various studies.

1. Factor V gene

1.1. Overview

Factor V is a protein that plays an essential role in the coagulation cascade. In the active form, Factor V aids in the conversion of prothrombin to thrombin and activated protein C plays an essential role in the inactivation of the activated Factor V. A mutated variant of Factor V is Factor V Leiden whereby glutamine replaces arginine at position 506 (or adenine replaces guanine at position 1691). Factor V Leiden confers resistance to activated protein C; therefor once activated, Factor V remains in the active form resulting in a potential hyper-coagulable state (Middendorf et al., 2004).

1.2. Results from the literature

The literature is full of studies providing positive correlation between Factor V Leiden and cases of thrombosis. A study in 2001 by Gurgey et al., demonstrated that 30.8% of 146 thrombotic patients with mean age of 36 years had Factor V Leiden (Gurgey et al., 2001). However, only 7.1% of the control subjects had the mutation. These thrombotic cases included venous as well as arterial thrombosis. A meta-analysis published in 2004 found a statistically significant association between ischemic strokes and Factor V Leiden with an odds ratio of 1.33 (95% CI, 1.12–1.58) (Soare and Popa, 2010). Approaching more the context of myocardial infarction, a meta-analysis on 191 studies was published in 2006 studying the correlation between seven gene polymorphisms and coronary disease. It compromised 66,151 cases and 91,307 controls. The per allele relative risk of Factor V Leiden for coronary disease was 1.17 (95% CI, 1.08–1.28) indicating a moderate association (Ye et al., 2006). Another meta-analysis showed a modest, yet statistically non-significant association between Factor V Leiden and arterial ischemic events with an odds ratio of 1.21 (95% CI, 0.99–1.49) (Kim and Becker, 2003). Studies providing association between Factor V Leiden and myocardial infarction per se were also published. A study in Munich containing 507 MI patients with an average age of 56.1 years and 404 controls with an average age of 54.4 years demonstrated a positive correlation with an odds ratio of 2.46 (95% CI, 1.35–4.50) (Middendorf et al., 2004). Both cases and controls contained similar proportions of males vs. females, with the males being more than the double. In another study, there were 560 men with first MI before the age of 70, and 646 controls matched by age. The odds ratio for the association between myocardial infarction and Factor V Leiden was however non-statistically significant, 1.4 (95% CI, 0.8 to 2.2) (Doggen et al., 1998).

In a meta-analysis study done by Diox et al., in 2003, there was no significant association between Factor V Leiden and myocardial infarction (OR = 1.25; 95% CI, 0.97–1.58). However, stratification by age revealed interesting results. Factor V Leiden was significantly associated with MI in patients < 55 years of age (OR = 1.48; 95% CI, 1.05–2.08) (Doix et al., 2003). Another study by Butt et al. (2003) showed similar results; in both cases and controls, Factor V Leiden showed a prevalence of 4.6%. However, it was found in 13.0% in early MI patients compared to 3.8% in older patients, and 4.8% in control subjects of similar age group (de Moerloose and Boehlen, 2007). In a study done by Tomaiuolo et al., there was no significant difference between cases of acute myocardial infarction (AMI) and the general population regarding the prevalence of Factor V Leiden, but there was a significant one between the cases of young AMI females and the general population with an allelic odds ratio of 3.67 (95% CI, 2.45–5.49) (Tomaiuolo et al., 2012). These results hint to the significant contribution of Factor V Leiden to early MI cases. In fact it is reported in the literature that among young patients and in addition to the classical risk factors for myocardial infarction, family history of myocardial infarction among first degree relatives constitutes a leading risk for MI (Sakowicz et al., 2013). A possible explanation is that in cases of early MI, classical risk factors have limited time to materialize in MI, and therefore genetic predispositions dominate and takeover (Sakowicz et al., 2013).

Evidence for this possible explanation has been reported in the literature. Middendorf et al., reported that the amount of atherosclerosis in MI patients heterozygous for Factor V Leiden is less than expected. For that, Factor V Leiden increases the susceptibility for MI early in the disease process (Middendorf et al., 2004). In another study, researchers did not find a significant association between Factor V Leiden and MI in