

Clinical research

Non-O-blood types associated with higher risk of high-grade atrioventricular block

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Abstract

Introduction: The non-O phenotype of the ABO genotype has been linked with an increased risk of cardiovascular disease. Atrioventricular (AV) block (AVB) is defined as retardation or cessation in the route of an electrical impulse passing from the atria to the ventricles because of an anatomical or functional disruption in the conduction system. We aimed to interpret the association between blood group status and high-grade atrioventricular block (HAVB).

Material and methods: This study was implemented as a retrospective review of the recorded data of patients diagnosed with high-grade AV block and a control group. The study population consisted of 640 patients with HAVB and 570 control subjects.

Results: Presence of non-O blood group ($p < 0.001$) was significantly more prevalent in HAVB patients than in the control subjects. Blood group type was the sole independent predictor of HAVB in multiple regression analysis ($p < 0.001$, OR = 1.35, 95% CI: 1.08–1.57). Also, third-degree AVB had a higher incidence in the non-O blood subgroup and also non-O blood group was a predictor of third-degree AVB ($p < 0.001$, OR = 1.39, 95% CI: 1.13–1.69). The incidence of HAVB did not distinguish between the two Rh (D) groups. Rh (D) status did not have an impact on HAVB.

Conclusions: This is the first study that has evaluated the potential relationship between HAVB and ABO blood groups. The main finding of this report is that patients with non-O blood group types have a higher risk for development of HAVB compared with O blood group patients.

Key words: atrioventricular block, blood type, fibrosis, genotype.

Introduction

Atrioventricular (AV) block (AVB) is defined as retardation or cessation in the route of an electrical impulse passing from the atria to the ventricles because of an anatomical or functional disruption in the conduction system. The conduction impairment can be temporary or permanent, with conduction that is delayed, intermittent, or absent. There are several types of AVB such as first-degree AVB, second degree AVB (Mobitz type-1

and type-2), third degree AVB, and advanced AVB. Commonly, AVBs other than first-degree AVB are accepted as high-grade AVB (HAVB) (i.e., necessary to evaluate for causes and treatment). The potential etiologies of HAVB are quite numerous and encompass reversible causes (both pathologic and iatrogenic) as well as idiopathic causes. Common potentially reversible causes include pathologic (acute or chronic myocardial ischemia, cardiomyopathy, myocarditis, endocarditis with abscess formation, hyperkalemia, hypervagotonia, etc.) and iatrogenic (medication-related such as AV nodal blocking medications, post-cardiac surgery, post-catheter ablation, post-transcatheter aortic valve implantation).

Other pathologic causes may be progressive or irreversible (e.g., infiltrative malignancies, neuromuscular diseases). However, in half or more of the cases, no specific reversible causes are identified, and the block is assumed to be secondary to the idiopathic progressive cardiac conduction disease with myocardial fibrosis and/or sclerosis that disturbs the conduction system. Congenital complete heart block is generally irreversible.

The ABO blood group is defined by the presence of A and B antigens on the superficial membranes of the red blood cells (RBCs). Furthermore, these antigens are widely embodied on the membranes of a wide range of cells, including platelets, vascular endothelium, and epithelium as well as in body fluids (such as in saliva). ABO blood groups have been related to various disease phenotypes, especially cardiovascular diseases. The most common etiologic causes of death in developed countries are cardiovascular diseases, and their prevalence rate is rapidly rising and evolving in developing countries. There have been considerable historical interrelations between non-O blood group status and an increase in some cardiovascular disorders. Recent genetic studies have described ABO as a locus for thrombosis, myocardial infarction, and multiple cardiovascular risk biomarkers, directing attention to mechanisms and potential for clinical advances. Progress in our comprehension of the physiologic enormity of various endothelial and platelet-derived circulating glycoproteins is illuminating the mechanisms through which the ABO blood group may identify overall cardiovascular disease risk. The role of blood group antigens in the pathogenesis of various cardiovascular disorders remains a captivating issue with the potential to lead to novel therapeutics and prognostics and to diminish the global burden of cardiovascular diseases.

Recently, there have been several reports showing that blood groups may play a role as an independent genetic risk factor predicting accelerated fibrosis. So, we hypothesize that blood types may

also be a predisposing factor for idiopathic HAVB which is associated with myocardial fibrosis and/or sclerosis.

Material and methods

This study was carried out as a retrospective analysis of the records of patients diagnosed with high-grade AV block in the emergency service and outpatient clinics at Kosuyolu Cardiovascular Research and Training Hospital and Gumushane State Hospital via the hospital information management system. Informed consent forms were taken from all of the patients and control subjects. Ethical approval was obtained from the institution's Ethics and Research Committee. Inclusion criteria were < 65 years old, non-congenital AV block, idiopathic HAVB, and a public ABO-Rh blood group. Patients with reversible cause-related HAVB (ischemia, cardiomyopathy, drug-induced, metabolic and electrolyte imbalance, iatrogenic) were excluded from the study. Age, sex, ABO-Rh blood groups, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, smoking, New York Heart Association (NYHA) class, stroke/transient ischemic attack, non-central nervous system embolism, and coronary artery disease were recorded. The distribution of ABO-Rh blood groups among HAVB patients was compared with Kosuyolu Cardiovascular Research and Training Hospital blood donors with normal atrioventricular conduction or first-degree atrioventricular block.

Laboratory analysis

ABO-Rh blood groups were defined by the lam agglutination technique using a blood grouping reagent (Dia-Gast, Loos, France), the microplate agglutination procedure using the Galileo System (Stratec, Frankfurt, Germany), or gel centrifugation assay using the IH-1000 Fully Automated System (DiaMed, Cressier, Switzerland).

Electrocardiographic evaluation

Second-degree (Mobitz type-1 and Mobitz type-2) and third-degree AV block, with or without accompanying bundle branch block, were considered high-degree AV block, and all arrhythmic events were arbitrated by a central committee.

Statistical analysis

Data are shown as mean \pm SD for continuous variables and as proportions for categorical variables. Differences between proportions were analyzed using the χ^2 test and substituted by the Fisher exact test when the expected cell count was < 5. Student's *t*-test analyzed differences between mean values. Variables with a *p*-value \leq 0.1 were

selected for logistic regression analysis. In order to describe any independent associates of HAVB, a logistic regression analysis was conducted. Statistical examinations were performed using SPSS version 13.0 (SPSS Inc., Chicago, Illinois). A two-tailed *p*-value of < 0.05 was considered significant for all analyses.

Results

The study population (*n* = 1210; 64.8% female) involved patients with HAVB (*n* = 640) versus the control group (*n* = 570) with a normal AV conduction time and first degree AVB. Blood group O was the most common phenotype (35.1%) followed by blood group A (24.5%), B (22.5%), and AB (17.9%). The majority of patients (65.7%) were Rh (D) positive, whereas 34.3% were Rh (D) negative. The detailed baseline patient characteristics are shown in Table I. Third-degree AVB (48.7%) was the most common HAVB type, followed by second-degree Mobitz type-1 AVB (32.3%) and second-degree Mobitz type-2 AVB (19.0%) (Table II). In the control group, normal AV conduction was 62.4% and in the remaining part of the control group was first-degree AVB (37.6%). Presence of a non-O blood group (*p* < 0.001) was significantly more prevalent in HAVB patients than in the control subjects. Blood group type was the sole independent predictor of HAVB on multiple regression analysis (*p* < 0.001, OR = 1.3, 95% CI: 1.08–1.57) (Table III). Also third-degree AVB had a higher incidence in non-O blood subgroup and also non-O blood group was a predictor of third-degree AVB (*p* < 0.001, OR = 1.39, 95% CI: 1.13–1.69) (Table IV). The incidence of HAVB did not differ significantly between the two Rh (D) groups. Rh (D) status has no impact on HAVB.

Discussion

The ABO blood group is established by the presence of A and B antigens on the surface membranes of the red blood cells (RBCs). Additionally, these antigens are widely present on the membranes of a vast cluster of cells, including platelets, vascular endothelium, and epithelium [1]. Moreover, they are secreted in saliva and body fluids [2].

Table I. Baseline characteristics of the study groups

Parameter	HAVB (<i>n</i> = 640)	Control (<i>n</i> = 570)	<i>P</i> -value
Demographic:			
Gender, female/male	422/218	362/208	0.234
Age [year]	57 ±10.8	53.9 ±11.1	0.198
Blood group type:			
O/non-O group	292/346	253/317	< 0.001
Rh positive	402	394	0.598
Medical history:			
Hypertension	219	231	0.548
Diabetes mellitus	31	29	0.687
Atrial fibrillation	39	32	0.79
NYHA III–IV	7	5	0.931
Stroke or TIA	8	6	0.927
Hyperlipidemia	242	240	0.621
Smoking	166	143	0.681
Non-CNS embolism	9	7	0.843
Coronary artery disease	234	209	0.841

Table II. HAVB types and incidence in the disease group

HAVB type	Percent of patient (%)
Third degree AVB	48.7
Second degree Mobitz type 1	32.3
Second degree Mobitz type 2	19

Table III. Predictors of HAVB in the HAVB patient group

Parameter	Univariate <i>p</i> -value	Multivariate <i>p</i> -value	OR (95% CI)
Non-O blood group	< 0.001	< 0.001	1.35 (1.08–1.57)
Age	0.423	0.283	0.958 (0.917–1.014)
Female sex	0.161	0.069	1.017 (1.005–1.031)
Hypertension	0.479	0.198	1.247 (0.673–2.342)
Coronary artery disease	0.198	0.139	1.437 (0.859–2.439)

Several previous studies have revealed that individuals with the non-O blood group had higher rates of cardiovascular events. Rumley *et al.* reported that patients with a non-O blood group have lower plasma levels of factor VIIIc and von Willebrand factors than the patients with blood group O; therefore thrombotic disease varies among them [3]. Kole described the relation be-

Table IV. Predictors of third-degree AVB in the HAVB patient group

Variable	Univariate <i>p</i> -value	Multivariate <i>p</i> -value	OR (95% CI)
Non-O blood group	< 0.001	< 0.001	1.39 (1.13–1.69)
Age	0.308	0.298	1.009 (0.879–1.312)
Female sex	0.129	0.092	0.903 (0.829–1.304)

tween ABO blood groups and cardiovascular disease risk profile in a general population-based meta-analysis [4]. Koster *et al.* showed that the risk of thrombosis rose with increasing vWF or factor VIII concentration and was higher in subjects of non-O blood groups than in those of group O [5]. Also, in another paper it was reported that patients with non-O blood groups have increased risk for venous thromboembolism [6, 7]. In a study which included patients with mechanical prosthetic valve thrombosis, Astarcioglu *et al.* detailed that non-O blood group was an independent risk factor for prosthetic valve thrombus [8]. In the Framingham study population, peripheral vascular disease was more prevalent in patients with a non-O blood group [9]. Koster *et al.* revealed that pulmonary embolism is more common in patients with a non-O blood group [5], and Clark *et al.* reported that the ABO blood group influenced the pathophysiology and prognosis in patients with cerebral ischemia of arterial origin [10].

Using genome-wide association studies (GWAS) in recent years has encouraged immense breakthroughs across almost the whole spectrum of cardiovascular diseases [11]. GWAS have confirmed *ABO* as a locus for venous thromboembolism (VTE), myocardial infarction (MI), and multiple cardiovascular biomarkers [11].

Also, it is detailed that the *ABO* locus may also play a role in the fibrotic/sclerotic process [11]. Recently there are reports about blood types and diseases in which there is a fibrotic process. Hakyemez *et al.* reported that blood types could play a role as a genetic risk factor for severe hepatic fibrosis and progression to cirrhosis [12]. Nikam *et al.* described that people with blood group B were at higher risk of developing oral submucous fibrosis as compared to other groups [13]. There is also some relationship with blood groups and fibrosis in cancer [14–16]. To our best knowledge, there has been no evidence about cardiac conduction system fibrosis with blood groups until now.

Atrioventricular (AV) block is defined as retardation or interruption in the route of an electrical impulse from the atria to the ventricles due to an anatomical or functional impairment in the conduction system [17]. The conduction impairment can be temporary or permanent, with conduction that is delayed, intermittent, or absent. In nearly all cases, the diagnosis of high-grade AV block

can be made in a patient with suggestive symptoms (e.g., fatigue, dyspnea, presyncope, and/or syncope) by obtaining a surface electrocardiogram (ECG), ideally a full 12-lead ECG but sometimes a single-lead rhythm strip is adequate if a full 12-lead ECG cannot be obtained. For the rare patient with a non-diagnostic surface ECG, invasive electrophysiological studies can definitively diagnose high-grade AV block and accurately identify the level of the block [17].

The potential etiologies of HAVB are quite numerous and encompass reversible causes (both pathologic and iatrogenic) as well as idiopathic causes. Common potentially reversible causes include pathologic (acute or chronic myocardial ischemia, cardiomyopathy, myocarditis, endocarditis with abscess formation, hyperkalemia, hypervagotonia, etc.) and iatrogenic (medication-related such as AV nodal blocking medications, post-cardiac surgery, post-catheter ablation, post-transcatheter aortic valve implantation) [18].

Other pathologic causes may be progressive or irreversible (e.g., infiltrative malignancies, neuromuscular diseases). However, the most common cause of acquired conduction system disease is idiopathic fibrosis [19]. There are two well-known forms of acquired idiopathic conduction disorder in the elderly population. First, Lev's disease results in sclerosis of the left side of the cardiac skeleton, and affects the branching His bundle [20]. Second, Lenegre's disease is thought to be a hereditary genetic disorder that can affect middle-aged people. This degenerative process involves the more distal portions of the bundle branches [21]. Both Lev's and Lenegre's diseases cause right bundle branch block and left anterior hemiblock in people without other cardiac abnormalities, and can eventually progress to complete heart block.

Since blood groups may play a role in the fibrosis process, we advanced the hypothesis that blood groups can also have a role in fibrosis associated with idiopathic atrioventricular block.

The main limitation of the study is that our study population is small. In future it can be evaluated in a larger study population.

In conclusion, this is the first study to evaluate the potential relationship between HAVB and ABO blood groups. We try to answer the question whether the relationship of blood groups with fibrosis in other system diseases is also efficient in

fibrosis associated with idiopathic atrioventricular block. The main finding of this report is that patients with non-O blood group types have a higher risk for development of HAVB compared with O blood group patients.

Conflict of interest

The authors declare no conflict of interest.

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