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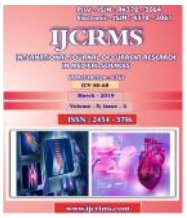

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An update on susceptibility of individuals to diseases based on ABO blood groups

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Abstract

Blood groups are phenotypic expression of the antigen present mainly in the red cells and some body fluids of an individual using corresponding antibody. ABO was the first set of blood group discovered and shows the highest clinical relevance in blood transfusion medicine. Researchers are concerned with ways of making life better for mankind and continue to look for improved methods of doing things. There is a strong relationship between the ABO blood group and some diseases. This paper was written to update the world on the association of ABO blood groups to susceptibility to some diseases.

Keywords: **S**usceptibility, diseases, ABO blood groups.

Introduction

The ABO blood group system is reported as the most clinically significant of all the blood group systems. This is because of the vast majority of the population carrying pre-formed ABO antibodies; this is the only blood group system where if you lack the antigen you will make the corresponding antibody without deliberate immunization (Mohandas, 2005). ABO antibodies can lead to intravascular haemolysis. If we were to randomly transfuse red cells to a group of people without ABO grouping either the donors or the recipients, there is a high probability that some would receive ABO incompatible blood and potentially undergo an acute haemolytic transfusion reaction. As such it is of paramount importance that both the blood donor and blood component recipient are ABO grouped correctly and compatible blood components are transfused (Mohandas, 2005).

The presence and lack of blood antigens in some blood groups cause blood membrane changes, morphologically and functionally. The structured dependent functions of blood types can associate the blood groups to health and diseases (Sandle, 1995).

History

History has shown that ABO blood types were discovered by Karl Landsteiner in 1901 when he worked on human serum derived from six scientists working in his lab, including himself

with serological methods, cross testing of sera and analysis of the agglutination (Owen, 2000). It was the first blood group system to be discovered. Landsteiner had mixed the sera and red cells from his co-workers and discovered that they reacted in different ways. He named three groups A, B and O. In 1902 Decastello and Sturli discovered the additional AB phenotype. From his experiments Landsteiner deduced that the lack of an A or B antigen resulted in the production of the corresponding antibody by the individual. This is known as 'Landsteiner's Law'. The ABO system is the only system where this phenomenon occurs. The first study on blood groups was performed by Ludwik Hirszfeld and his wife, Hanka in a large number of soldiers during World War I at the Macedonian front. They found that soldier's blood types were differently distributed; soldiers from North Central Europe were more common in A type, but B type was prevalent in Eastern Europe (Okroi *et al.*, 2000). The first scientific article that discussed the relationship between blood types and diseases was published in 1917 and revealed the association of ABO blood types and tuberculosis. Later, many studies supported the hypothesis that ABO blood types could be related to the infectious diseases (Liumbruno *et al*., 2013). Many things in happened in the past in relations to different diseases which eluded my efforts and may be attributable to the blood groups based on the genotype of the blood group predisposing the individuals to certain diseases.

ABO Blood types

The ABO blood type is the main type of blood group. The human blood type grouping is involved in three carbohydrate antigens (ABH). AB blood type depending on glycosyltransferase activity that converts H antigen into A and B antigens. The transferase activities of A and B alleles are different because of a single-base replacement in A and B genes and four amino-acid residues. The *O gene* consists of a single-base deletion that produces an inactive protein which fails to convert H antigen (Yamamoto *et al*., 1990). Therefore, individuals expressing N-acetyl D- galactosamine transferase and D-galactose are group A and B, respectively (Dean , 2005). Rh (Rhesus) blood group is the most important group after ABO blood type in transfusion medicine. It is also a major player of hemolytic disease of the newborns (HDN) (Dean , 2005) often called Rh disease. The Rh blood group antigens (D and Cc/Ee) are encoded by two highly related genes, RHD and RHCE located on 1p36-p34 (Cartron, 2010) that represents RhD-positive phenotype to individuals.

ABO blood grouping is crucial for safe blood transfusion

The discovery of the ABO blood group system was made when Landsteiner separated the cellular components from the liquid components of blood and observed the agglutination of RBCs in certain combinations upon mixing. Based on the agglutination patterns, he categorized the subjects into three groups. In the next year Decastello and Sturli discovered the fourth group, and these four groups became the ABO blood groups. In order to explain the agglutination patterns, Landsteiner postulated that there were two antigens (A and B) and two antibodies against those antigens (anti-A and anti-B). He assumed the presence of the antibodies in the sera of individuals who did not express those antigens, which was later named Landsteiner's Law. His understanding was an important step toward the safe practice of blood transfusion, where transfusion should be performed between individuals whose blood components would not agglutinate upon mixing. It was reasonable to assume that the hemagglutination due to mismatch would also occur inside the body if it occurs in the test tube. Therefore, ABO typing before any transfusion was logical. To crossmatch also was wise because unknown antigens or antibodies could be present. Because the readers of *Immunohematology* are familiar with safe practice of blood transfusion and the techniques used for ABO typing. It is important to note that subgroups have been identified, based on the different degrees and patterns of agglutination, using standard RBCs and antibodies. Those subgroups include A2, A3, Ax, Ael, B3, Bx, and Bel. The natural antibodies seem to occur due to constant or occasional immunologic stimulation by substances, such as food, pollen, and bacteria that are ubiquitous in nature.

ABO Genetics

The ABO gene locus is on chromosome 9. At its most basic, one of three allelic gene options are possible; *A* or *B* or *O*. *A* and *B* are codominantly expressed; *O* is amorphic. The gene product is an enzyme; A or B transferase, which requires the presence of H antigen in order to act. This means the ABO genetic pathway is also dependent on inheritance of the *H* gene of the H blood group system. The H blood group system is separate and independent from the ABO system, residing on chromosome 19. The H antigen is high prevalence occurring at a frequency of 99.9% in all populations.

Evidences for association of ABO blood types with different diseases

Cardiovascular disease

Von Willebrand factor (vWF) involves in homeostasis and thrombosis by taking part in platelets aggregation and adhesion at vascular damage sites (Ruggeri, 2007). It is also a carrier for factor VIII (FVIII) and protects this factor from proteolysis degradation. The plasma level of vWF was clinically used for estimation of cardiovascular risk and for determination of arterial thrombosis (Spiel *et al*., 2008). The ABO blood groups and their locus are important genetic factors that affect the plasma level of vWF. It has been shown that increased risk of cardiovascular disorders in non-O individuals can be attributed to the plasma level of vWF. Interaction between ABO blood group antigens and vWF participates in vWF-related diseases such as cardiovascular disorders (Franchini *et al.*, 2007). It was reported that non- O blood groups (A, B, and AB) have 25% higher level of vWF than O blood type. This is due to high capacity of O blood type in cleaving by protease, a disintegrin and metalloproteinase with a type 1 motif, member 13 (ADAMTS13). ABH blood group antigens are expressed and identified on N-glycan chains of circulating vWF which plays a major role in vWF clearance (Jenkins, 2006). The presence of the N-glycan oligosaccharide chain on the vWF is important for interaction between vWF and ADAMTS13. In other words, the N-glycan chain may induce a conformational change and modulates this interaction by flanking to the cleavage site. Consequently, N-linked glycan chains limit interaction capability and prevent vWF from ADAMTS13 proteolysis. P-selectin and intercellular adhesion molecule-1 (ICAM-1) are adhesion molecules that participate in inflammatory process and cardiovascular diseases. There is different single nucleotide polymorphisms (SNPs) in P-selectin and ICAM-1 genes that are associated with *ABO gene* variants (Barbalic, 2010). ABO blood group affects the soluble level of P-selectin and ICAM-1 during the interaction between glycosylated antigens and P selectin and ICAM-1 (Barbalic, 2010). Soluble ICAM-1 (sICAM- 1) presents in plasma is an inflammatory marker and correlated with different disorders like heart disease and myocardial infarction.

Infectious diseases

The likely relationship between infectious agents and ABO blood antigens is linked to its carbohydrate moieties on RBC surface. This structure may function as a receptor for some viruses, bacteria, and parasites and mediate their entrance (Borén , 1993). Some parasites cannot bind to RBCs that lack other blood group antigens, thus, these are important structures for adherence (Garratty, 2005). This was approved in Norwalk virus (NV) infection which is more common in blood type O but individuals with blood type B are resistance to NV infection. This ability may occur due to the expression of ABH carbohydrate antigens. The existence of terminal α-galactose can modify the NV ligand and make it hidden for NV binding and block the binding site. Lack of ABH antigens expression in O lead to susceptibility of individuals to infection after exposure to NV. In the same way, histo-blood group antigens (HBGAs) B were protected against Noroviruses (NoVs) gastroenteritis by interfering with virus binding to H antigens. The association between hepatitis infection and blood group antigens is not exactly determined. There are different studies with variety of results so more improvements are needed. It was reported that A blood type was associated with HBV (hepatitis B virus) infection and pancreatic cancer

in a synergistic manner (Wang DS, 1993). Aljooni *et al* observed a significant association between ABO blood type and hepatitis infection. They indicated that HBV and HCV (hepatitis C virus) infections were high in O blood type but low in AB. Similar results were reported by Behal *et al* who found variation in susceptibility to HCV infection among ABO blood groups. High seroprevalence of HCV were seen in people with O, but the lowest level was detected in AB blood type. They did not find any significant association between infection with HBV and ABO blood types. Some infections, including HBV, HCV, HIV, and syphilis were analyzed for their relationship with blood groups in a study conducted among Iranian individuals. The results showed low frequency of blood group B in HBV infected patients and significant association between A blood group and HIV infection. They also found no correlation between Hepatitis C and syphilis infections and ABO blood groups system (Mohammadali, 2014). Woo *et al* showed that non-O blood types were at increased risk for hepatitis C virus and pancreatic cancer but similar association was not observed for HBV infection. These results were also found in a study conducted by Shavakhi *et al*. They suggested non-O blood groups as genetic risk factors for HCV infection and liver fibrosis progression. The same results were also found in another study performed by Poujol-Robert *et al. The* high percentage of hepatitis B- surface antigens diagnosed in the blood group A proves HBV is more prevalent among A than other types. In one study, a high level of HBsAg was observed in blood group A negative and HCV and HIV infections were more prevalent among O negative donors. The same analysis was performed on 6000 donors and came to a conclusion that blood group A negative was more susceptible to HIV and HBV but blood group B negative was influenced by HCV Recently, different results were found in a study that reported high prevalence of HCV in individuals with blood group B. one analysis, subjects with O "positive" blood group were found to be common in blood donors who are affected by HIV, HBV, and HCV (Dirisu *et al*., 2014). The same results were previously reported by Sayal *et al*. Recently Onsten *et al* proved the high frequency of blood type B among HIV patients through its mechanism: B blood type has limited antigen recognition ability of galactosylα1-3 galactose(Galα1-3Gal) and antigen binding capacity of anti-A antibody. Other mechanisms are involved inglycosylation patterns of HIV envelop. Blood type glycosyltransferase add ABO glycan structure to glycoprotein 120 (gp120) and invade from recognition of immune system and neutralizing antibodies by masking within host glycans (Onsten, 2013).However, Dirisu *et al* determined high prevalence of blood group O "positive" among HIV, HBV and HCV (40). In another study, high rate of HIV-2infection was reported for blood group AB (Abdulazeez, 2008). The results from the investigation of the correlation between ABO blood groups and influenza virus indicated that blood group AB subjects are more susceptible to influenza A and B with high rates of attacks (Aho *et al.*, 1980).The presence of A and B antigens and acting as a receptor is not only limited to virus but also found in parasites such as *Plasmodium falciparum*. *P.falciparum* can lead to severe form of disease through parasite virulence factor like rosetting that blocks microvascular blood flow. A and B trisaccharide structure antigens act as a receptor for rosettes formation on erythrocytes. Lack of terminal glycosyltransferases activity causes blood type O to be a structurally disaccharide and possesses lower rosetting ability. It forms small and reduced rosettes effect that is easily disturbed. Therefore, individuals with blood group O may be protected against severe malaria (Rowe, 2007).Individuals with group O were observed to constitute a large number of cholera patients with significant differences to other patients (Barua , 1977). In one study, cholera infected patients were two times more likely to be the blood group O. The possible mechanism is that the A and B blood group carbohydrates interfere with binding of cholera toxin to its intestinal receptor (ganglioside GM1).*Toxoplasma gondii*(*T gondii*) is a protozoan parasite that infects human and causes toxoplasmosis. *Toxoplasma gondii*(*T gondii*) the causative agent for human toxoplasmosis is a protozoan parasite. Toxoplasma latent infection induces behavioral changes in rodent and human hosts. The latent toxoplasmosis-personality

profiles consist of reduced psychomotor performance and increased reaction time of traffic accidents, possibly related to the levelof dopamine and testosterone. It was found that RhD phenotype can modulate the latent infection effects probably via membrane pump of red blood cells (50). It was also shown that Rh-positive individuals are protected against the *T. gondii* induced personality trait changes (Flegr, 2010).

Diabetes

There are conflicting results reported by different researchers on the hypothesis that there is an association between ABO blood types and diabetes. In one research, a strong relationship of diabetes mellitus with blood groups, especially A, AB and Rh positive was found (Sidhu *et al.,* 1988). The increased frequency of diabetes mellitus among B blood type may prove this association. It was also indicated that blood type AB has low distribution. Similarly, high frequency of blood type B was detected among patients with diabetes mellitus but distribution of blood type O was low. Similar results were achieved from a large cohort study evaluating the involvement of ABO blood types and Rhesus facto r(and the combination of both) in development of type2 diabetes mellitus. It was also found that blood type O had a lower risk of type 2 diabetes mellitus (Fagherazzi *et al.*, 2015). In another investigation, blood type B was more prevalent in diabetic patients while blood group O was less affected (Bener, 2014). Significant association between blood type B and diabetes was reported in a research conducted in Iran, which is consistent with other investigations (Ganesan *et al.*, 2014). In contrast, Waseem *et al* suggested a negative relationship between blood groups A and B and diabetes since they were less common in diabetic patients. They also found high frequency of blood group AB in diabetic group. They attributed these incompatible results to different ethnic and geographical factors and small sample size (Waseem *et al*., 2012). Considering all studies, some researches believed that ABO blood types were not really related to diabetes mellitus (Sharma *et al.,* 2015).

Cancer

The expression of blood group antigens alters during the process of cell differentiation and malignancy. Lack of A and B antigens resulted in promotion of cell motility, proliferation, invasion, and metastatic tumor formation (Dabelsteen *et al*., 2014). Cancer is abnormal proliferation of different kinds of cells in the body and is categorized into three groups (carcinomas, sarcomas, and leukemia or lymphomas) based on the primary types of cell where cancer cells originate. The most prevalent form of human cancers is carcinomas that are the malignancies of epithelial cells. Most of the epithelial and endothelial cellscan express ABO blood antigens which are normally present on the red blood cell . ABO blood antigens are carbohydrate structures relating to the cell-surface glycolipids and/or glycoproteins. Tumor development and progression are correlated with glycosylation modification. The expressions of blood group antigens are different in human normal tissue and carcinomas; while the type of differentiation of the epithelium determines ABO antigens, they are decreased in carcinoma such as oral carcinoma Possible mechanisms by which blood antigens relate to cancers includes hyper methylation of ABO gene promoter (Dabelsteen *et al.,* 2005), loss of heterozygosity (LOH) at ABO locus at chromosome 9q34 (Gao *et al.,* 2009), variant ABOalleles and SNPs (i.e. SNPs correlated with TNF-α)(Rizzato *et al.*, 2013), and presence of H blood-group antigens onCD44 adhesion molecule (Hallouin *et al*., 1997). It was statisticallyproved that ABO gene variability can affect glycosyltransferase expression and activity and result cancer development. These mechanisms decrease the activity of glycosyltransferase and increase tumor progression, metastasis, and migration. For example, methylation in A promoter lead to changes in A transcription and expression level; on the other hand, A (also B and H) expression is correlated with tumor proliferation and metastasis (Sarafian V, 1993), therefore is definedas a possible mechanism in ABO antigens-related cancers by controlling the A expression and activity (Iwamoto *et al.*, 1999).

Thus, human ABO (H)blood antigens possess carbohydrates, which contribute in different cell events such as cell proliferation and tumorigenesis; maybe they can be correctly named as "tumor-associated markers" (Sarafian *et al.*, 1993).Class 1 carcinogen has been attributed to *Helicobacter pylori* (Hp) because of its role in gastriccarcinogenesis. Severe gastritis, glandular atrophy, and intestinal metaplasia are the results of chronic *H.pylori* infection. VacA, CagA, and blood groupantigens are gastric adenocarcinoma-associating factors (Prinz *et al*., 1903). The perquisite step for Hp infection is its colonization on mucosal surface and invasion to the epithelium which needs to interact with glycan structures. Attachment of Hp to the stomach epithelial lining is mediated by fucosylated blood group antigens. The ABO glycol conjugate antigens facilitate Hp intracellular adhesion by acting as a receptor for binding to the outer membrane protein, BabA, *H. pylori*. This attachment leads to release of virulence factor such as CagA into them cytoplasm of host cells. This initiates IL-8 secretion and its inflammatory response, increasing cell proliferation and migration. The association between A blood type and gastric cancer was confirmed in different studies (Edgren ey *et al*,. 2010).

Personality traits

There are many studies that proved the association between blood groups and personality traits. Obsessional personality traits were analyzed among 600 individuals, and the results showed high incidence of A type and low incidence of O in obsessive compulsive patients (Rinieris *et al*., 1980). A similar analysis was recently performed in Iran that failed tofind any significant relationship between blood types and personality traits (Dibajnia *et al*., 2014). In another study, significant incidence of A phenotype was found in patients suffering from hysteria (Rinieris *et al.*, 1978). The relationship between blood group and mental health was demonstrated in a study which revealed ABO blood types were associated with schizophrenia and different types of depressions. In addition blood type O is believed to be tightly linked with depression and evolutional depression (Rinieris, 1978). Therefore, ABO blood group may affect the human's traits and habits. Hobgood investigated the possible link between blood groups and personality traits (Hobgood., 2011). The author hypothesized that personality traits were correlated with catecholamine genes. On the other hand,catecholamine genes such as COMT catechol Omethyltransferase(COMT), monoamine oxidase A(MAOA), and dopamine beta hydroxylase (DBH),were associated with ABO blood groups (Goldin *et al*., 1982).Because DBH locus was found to be in linkage disequilibrium with ABO genes on chromosome9q34 (Goldin *et al*., 1982), so other catecholamine genes may act similarly. Hobgood classified ABO blood types and attributed the traits to them, which were consistent with the pattern of catecholamine genes activity. He found that A blood type was correlated with non-submissiveness, non-perfectionism, and non-aggressiveness. B phenotype was correlated with submissiveness, perfectionism, and nonaggressiveness on the basis of the level of catecholamine. With the same reasons, blood type O was correlated with non-submissiveness, non-perfectionism, and aggressiveness (Hobgood, 2011).

Conclusion

ABO blood group has been shown to a highly of clinical relevance in transfusion medicine. This contributes to transfusion reactions that are highly dangerous when presented due to incompatibility and haemolytic disease of the new born. There is a strong link between ABO blood group and susceptibility to diseases. Individuals with a particular ABO blood group are more predisposed to certain diseases more than persons with other ABO blood groups.

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