REVIEW ARTICLE

ABO BLOOD GROUP SYSTEM: IN THE CONTEXT OF HUMAN DISEASES

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ABSTRACT

Background: The expression of ABO blood group antigens on red cell surface and a variety of human cells, tissues and fluids is well documented. Studies in the recent times have reported association between these blood group antigens and some disorders in man. Cancer, Cardiovascular disease and infection are some of the disorders reported. The interplay has given rise to the assertion that ABO blood group system has extended its clinical significance beyond the natural frontier of transfusion Science. This narrative review aims at summarizing information concerning the role of these blood antigens in the pathogenesis of human disorders such as cardiovascular, cancer and infectious diseases. **Methodology:** Literature on the role of ABO blood group antigens in human disease was searched from BMCMed, PubMed and text books. The search words were ABO blood group antigens, cardiovascular disease, Von Willebrand factor, cancer, infectious disease, and neuroscience. We reviewed, evaluated and summarized the relationship between these disorders and ABO blood group; and possible pathogenic mechanism involved. **Conclusion:** It is now known that non – O blood group antigens are linked with the risk for cardiovascular disease, oncological states and infectious disorders. However further studies are needed to elucidated molecular mechanism/s in the interplay between these antigens and human health. This may as well elevate ABO blood typing as a veritable tool for cardiovascular and oncologic disorders risk assessment.

Keywords: ABO blood group antigens, Disease, Cancer, Cardiovascular, Health

INTRODUCTION

ABO blood group antigens are complex carbohydrate molecules on the extracellular surface of red blood cell (RBC) membranes.[1,2,3] The A and B alleles encode different glycosyltransferase enzymes that add N–acetyl galactosamine and D–galactose to a common precursor side chain (the H determinant) which becomes converted into A or B antigens respectively.[4,5,6] The O allele does not encode a functional enzyme, as a result the OO genotype lack these transferase, and so a solitary terminal fructose moiety is attached to the precursor oligosaccharidechain giving rise to unaltered H structure which represents the phenotype O blood group.[7,8]

Apart from its expression on RBC surface, the antigens of ABO blood group are also present efficiently on other human cells and tissues. These include epithelium, sensory neurons, vascular endothelium and platelets.[9,10] This fact explains the extension of the clinical significance of the ABO blood group beyond the traditional boundaries of immune-haematology and transfusion science. The apparent involvement in the pathogenesis of a significant range of human diseases, are adequately

exemplified by cancers.[11] Cardiovascular diseases[12]and infections.[13,14] Recent researchers have also attempted to niche out a role for ABO blood group antigens in neuroscience, implicating these antigens in the developmentence-phalomyelitis.[15]

This review therefore aims at bringing to light once more the relationship between human health and the antigens of ABO blood group beyond transfusion medicine. This may stimulate further researches that may unravel the molecular mechanism/s therein.

MATERIALS AND METHOD

Literature on the role of ABO blood group antigens in human disease was searched from BMCMed, PubMed and text books. The search words used were ABO blood group antigens, cardiovascular disease, Von Willebrand factor, cancer, infectious disease, and neuroscience. We reviewed, evaluated and summarized the relationship between these disorders and ABO blood group and the possible mechanism involved

Cardiovascular diseases and abo blood group

In the past four decades' literature, have emerged consistently describing a relation between ABO group antigens and cardiovascular disease.[2,3,8,10] In a systematic review and Meta-analysis, Dentali *et al*,[16]documented that a non-O blood group individuals have approximately 2-fold increased risk for venous thrombosis. The same authors found a weaker but significant association for arterial thrombosis with an odd Ratio (OR) of 1.28 for myocardial infection and OR 1.17 for Ischemic stroke. The major underlying mechanism proffered to explain this association was the immense influence ABO blood group system has on haemostasis and more importantly on pro-thrombotic risk factors Von Willebrand (VWF) and by extension factor VIII.[17,18] It is now well documented that individuals of non – O blood group (A,B, AB) have levels of both VWF and FVIII approximately 25% higher than that present in the O blood group individuals.[19,20]

The molecular basis of these events is hinged on the presence of ABH structure in the VWF n-linked Oligosaccharides,[20] which modulates the activity of the circulating VWF through different levels of glycosylation. It is suggested that the addition of A or B terminal carbohydrate antigen to VWF in the endothelial cells might influence synthesis/secretion, levels, function and clearance of this procoagulant factor or modify its biological activity.[20,21]

Venous and Arterial Thrombotic Events

There exist in the literature consistent information concerning the ABO blood group antigens related risk of venous thrombotic events.[16,22,23] Wauthrecht *et al*.,[22] in a study with 369 diagnosed and confirmed deep vein thrombosis patients found a significantly high frequency of non-O blood group as compared with the frequency in 49,373 healthy blood donors (70.6% vs 53.9%). Vasan*et al*,[25] in a case control study of more than 300 consecutive patients diagnosed with episode of venous thromboembolism (VTE), reported that blood group O was less represented among the VTE patients compared to the controls (25% vs 43%). They went further to report that the group O subjects had lower concentrations of both VWF and FVIII as compared to those of the non-O (A,B, AB) individuals.[3,23] These appear to further clarifies the relationship between ABO blood group, VWF, FVIII and the pathogenesis of VTE[3]. In a subsequent study by Dentali and Colleagues[16] involving a larger number of studies and VTE cases (38 studies with 10,305 VTE cases) the outcomes were comparable to previous reports with a cumulative odd ratio OR of 2.08 recorded.

A less consistent data is available in the literature regarding ABO blood group relationship with arterial thrombosis; with a few revealing statistically significant associations.[2,3,24] In ten years' prospective study Senthil and colleagues found an association between ABO blood group and arterial thrombotic event especially in older subjects. In a large study involving 1.5 million subjects Senthil*et al*,[25] reported 25,653 arterial events and 9,170 venous events occurring in 1,112,072 individuals during 13.6 million person-year of follow up. In comparison blood group O, the non-O groups (A,B, AB) were strongly associated with higher incidence of both venous and arterial thromboembolic events. In a relatively recent work, Djibril and colleagues[26] investigated cardiovascular disease and ABO blood group in African subjects and concluded that group

A individuals had higher incidence of Ischaemic disease and coronary artery disease in sub Saharan Africans. This assertion is supported by evidence indicating that elevated VWF-FVIII levels are risk factor for coronary heart disease (CHD).[27] To this end further clarification was provided by Genom-Wide-Association Studies (GWAS) which documented that variants at ABO Loci are associated with increased levels of plasma lipid and inflammatory markers such as soluble intercellular adhesion molecule I, E-selectin, P-selectin and tumour necrosis factor-alpha.[28-32] Also in a prospective cohort study recruiting several thousands of participants, assertions were made that non-O blood group had an 11% relative risk of developing CHD compared to O blood group individuals.[3,33]

Cancer and abo blood group

Medical/scientific literature in the past 5 decades have revealed relationship between ABO blood group types with some oncological disorders and the most important representations are given by Gastric and pancreatic malignancies.[2,3]

Gastric Cancer

Gastric cancer is adduced as the fourth most common malignancy in the world, and the second leading cause of cancer mortality.[3,34]

In 1953 Aird and colleagues[38] reported the first realistic study relating ABO blood group and gastric cancer. They employed a study population of 3,632 patients with cancer of the stomach in various hospitals in England and Scotland. Controls were enrolled from the same localities. The report from this study showed a 20% increase of carcinoma of the stomach in group A as compared to group O individuals. In the early 1960's a combine analysis on gastric cancer cases in 15 study locations in the USA, Europe and Australia reported significantly positive association between non-O blood group and the risk of gastric cancer with an odds ratio (OR) of 1.24 (95%C1) for patients with blood group A compared to those with blood group O[35,36]. In two more subsequent studies by Edgren and colleagues[36] and Wang and co-workers[37] employing very large study population a consistent conclusions confirmed that blood group A is indeed associated with a higher risk of gastric cancer compared to blood group O. Wang and colleagues went further to expatiate that subjects with non-A group (B and AB) had lesser risk for gastric cancer that individuals with A blood group (OR: 1.34). They interestingly also found that the ratio of Helicobacter Pylori infection in the blood group A patients was significantly higher than in non-A blood group subjects (OR: 1.42).[2,3] Previously literature revealed a link between H. Pylori infection status, ABO blood group type A and gastric precancerous lesions.[36]

Pancreatic Cancer

Pancreatic cancer, one of the most aggressive types of cancer with a very high mortality rate is the seventh most frequent cause of cancer death worldwide.[34,37] For more than 40 years the association between ABO blood group and risk of pancreatic cancer has been known; however, it is not until the work of Aird *et al*,[38] in the early sixties that greater attention was given to the relationship. These authors landed some strength to existing knowledge that cancer of the pancreases is commoner in persons of group A than in persons of group O or B. Since after the report of Aird and colleague's literature is awash with reports strengthening their observation.[39-45, 70] In a recent study in the USA it was observed that in comparison to group Opatients' non-O blood group had an adjusted hazard ratio for pancreatic cancer of 1.44 (95% C1]) and therefore were more likely to develop this cancer.[12]

Additionally, in 2009 Multinational Pancreatic cancer cohort consortium (PanScan) in association with GWAS identified pancreatic cancer susceptibility loci in the ABO gene. In their study, 1896 individuals with pancreatic cancer and 1939 controls were genotyped and a significant association was reported for rs505922, a single-nucleotide polymorphism which map to the first intron of these ABO genes.[42]

An interesting study by Wolpin and colleagues in 2010[44]suggested a role for ABO glycosyltransferase specificity in pancreatic tumorigenesis asserting that A^1 allele (corresponding to increase glycosyltransferase activity[13] confers greater

pancreatic cancer risk than A^2allele. A^1 has been shown to have greater glycosyltransferase activity than A^2blood group.[3]

Other types of Cancers

Researchers have come up with reports associating other types of cancer with ABO blood group. Data from large prospective cohort studies reported that ABO blood group system is associated with cancer of the lung, skin and ovary while no association was found with breast and colon cancers[3]. Lee et al.,[46] confirmed blood group A antigen asa favourable prognostic marker in non–small–cellLung cancer; while Xie J and colleagues[47]found a higher incidence of skin cancer in the non-O blood group compared to the O blood group. In a report published in International Journal on cancer, Gate *et al.*,[48] documented a significant incidence of epithelial ovarian cancer in non-O blood group individuals compared to the group O individuals. In addition, a higher risk for renal cell cancer was found in non-O blood group also; this was mostly in woman.[49] For these other types of cancers, Giancarlo and Massimo[3] in a narrative review opined that additional studies are needed to confirm the association detected and to explore the mechanism/s through which ABO blood group may influence them.

INFECTIOUS DISORDERS

The first publication concerning infectious diseases and ABO blood group antigens was published a hundred (100) years ago.[3,50] Infections of bacteria, parasites and viruses later were reported by various authors in relationship to ABO blood group antigens.[51] The association with malaria parasite was more reported. Evidence exists that supported the opinion that blood group O provides a selective advantage against severe malaria.[52-55] It is believed that ABO system glycosylation particularly with A antigen terminal sugar and infected RBCs provided support for rosette formation with uninfected cells, this phenomenon promotes vaso-occlusionin severe malaria disease.[3,52,53] Panda and colleagues[55] in a case controlled study and meta-analysis reported and confirmed a significant protective effect of group O against severe malaria. They also demonstrated a significant association of blood groups A and AB (not B) with severe malaria. The formation of rosette forming phenomenon was least observed with blood group O suggesting that the prevalence of this blood group in malaria endemic area is in line with the concept of evolutionary selective geographical distribution of ABO blood group.[53]

Another study in Ghana West Africa by Timmann *et al.*,[54] via genomic- wide–association study (GWAS) confirmed the association between ABO polymorphism and incidence of severe malaria. They unmasked two previously unknown Loci associated with severe falciparum malaria in patients and controls. One of the Loci was identified on chromosome 1q32 and another on 16q22. These they reported encode genes which control calcium pump of red blood cells and microvascular endothelial integrity which becomes damages when parasitized erythrocytes adhere to it.[3]

H. pylori infection is now known to aid susceptibility to gastro – duodenal disease.[57] Various authors have confirmed that Helicobacter pylori infection in blood group A patients were significantly higher than in non-A blood group subjects.[56-58] Rizzato *et al.*,[45]went further to confirm that H. pylori infection association with gastric cancer is highly dependent on H. pylori cytotoxic – associated gene A (CagA) status. The latter is responsible for the secretions of the CagA virulence protein that is injected in the cytosol of host cell and can play a relevant role in the development of pre-cancerous lesion.[2,3,36] Much earlier in 1994 Swerdlow and colleagues[59]documented in Peru Latin America that an association was found with blood group O and severe form of cholera.

One of the most recent examples of viral disease statistically linked to ABO blood group is Chikungunya virus infection.[60,61] Liumbruno and colleagues[3] however opined that the putative association needs re-evaluation and confirmation. Susceptibility to norovirus infection a common cause of gastroenteritis in man has also been linked to the expression of ABH and Le antigens in the gastrointestinal tract.[3] Tan and colleagues[62] proposed that association of ABO blood group antigen with susceptibility to norovirus infection may be strain – specific rather than Geno group dependent.

Inhibition of retrovirus infection by natural Anti A/Anti B antibodies of ABO blood group system has been documented; this however was supported only by invitro observations in experimental platform.[63] Further research in these direction hopefuls may in-part cast more light on discordance outcome that follow HIV exposure in some cases.

The area of neuroscience and association with ABO blood group is not left out in this intriguing relation of blood group antigens and human disease. Mollicone and Co-workersdescribed the expression of B and H antigens on the primary sensory cells of the rat olfactory organ and inner ear.[64] After this initial report, several authors have written reports associating ABO blood group antigens with sensory neurons in both the main and accessory olfactory systems.[64, 65, 66, 67] St John et al,[66] related A carbohydrate glycosylation in the expression and development olfactory system. This assertion was later affirmed by the report of Chehrehasa and colleagues.[67]

CONCLUSION

Despite our enormous knowledge about the complexities of ABO blood group system, its relationship with human diseases in still not completely understood; because information continues to emerge to elucidate the interplay between the blood group system and human health. The association of non-O blood group and increased mobility and mortality is well documented for cardiovascular events, and oncological conditions such as gastric and pancreatic cancers. For infections, it is now understood that blood group O appears to have a better outcome in the case of severe malaria infection. However, more studies particularly in area of genomics are needed to completely unmask the molecular mechanism linking ABO blood group system and the statistical association document for some disease conditions. If that is achieved blood group antigen typing may become a veritable tool in human disease monitoring and diagnosis.

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