

ВНУТРЕННИЕ БОЛЕЗНИ INTERNAL DISEASES

THE INFLUENCE OF BLOOD GROUPS ON PREDISPOSITION TO CERTAIN DISEASES: MOLECULAR MECHANISMS AND CLINICAL IMPLICATIONS (BRIEF-REVIEW)

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RESUME

The problem of early diagnosis and detection of diseases predictors of various etiologies is relevant. Blood type can act as such a predictor. The research for the relationship between blood type and predisposition to certain diseases will make it possible to identify risk groups for a particular disease and develop preventive measures. One such predictor could become blood type. The relationship between infectious (Cholera, the plague, tuberculosis, smallpox etc.) and non-communicable (oncological, neurodegenerative, cardiovascular, dental diseases etc.) ABO blood type and other systems such as Rhesus, Lewis is being discussed. Although considerable advancements have been achieved in investigating the mechanisms that facilitate this connection, the inquiry remains unresolved. This review examines the current state of the problem and the alleged mechanisms of the association of various blood groups with a predisposition to certain diseases. The relationship between blood type and oncological diseases has been most studied. The relationship of blood type is discussed not only with certain diseases, but also with typological personality traits, temperament, and response to stressful factors that can predispose to the development of somatic and mental illnesses. Studying the influence of blood groups on predisposition to the development of dental diseases is largely devoted to the relationship of blood type ABO with periodontal health. There are studies examining the prevalence of caries in people with different blood types. We analyzed more than 100 articles indexed in RSCI, PubMed, and Scopus, mainly over the past 10 years. Forty eight sources were used for the article, of which 16 were published in the last 5 years. Works published earlier than 2005 were excluded from the analysis.

Key words: blood groups, antigens of the ABO system, predisposition to diseases, infectious, somatic and dental diseases, blood

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ВЛИЯНИЕ ГРУПП КРОВИ НА ПРЕДРАСПОЛОЖЕННОСТЬ К НЕКОТОРЫМ ЗАБОЛЕВАНИЯМ: МОЛЕКУЛЯРНЫЕ МЕХАНИЗМЫ И КЛИНИЧЕСКИЕ ИМПЛИКАЦИИ (КРАТКИЙ ОБЗОР)

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РЕЗЮМЕ

Проблема ранней диагностики и выявления предикторов заболеваний различной этиологии является актуальной. Группа крови может выступать в качестве такого предиктора. Поиск взаимосвязи между группой крови и предрасположенностью к определённым заболеваниям позволит выявлять группы риска по конкретному заболеванию и разрабатывать профилактические меры. Обсуждается взаимосвязь между инфекционными и неинфекционными заболеваниями и группой крови АВ0 и другими системами, такими как резус-фактор, система Льюиса. Несмотря на значительный прогресс в изучении механизмов реализации этой взаимосвязи, вопрос остаётся открытым. В обзоре рассматривается современное состояние проблемы и предполагаемые механизмы связи различных групп крови с предрасположенностью к определённым заболеваниям. Наиболее изучена связь между группой крови и онкологическими заболеваниями. Обсуждается связь группы крови не только с определёнными заболеваниями, но и с типологическими чертами личности, темпераментом и реакцией на стрессовые факторы, которые могут предрасполагать к развитию соматических и психических заболеваний. Исследование влияния групп крови на предрасположенность к развитию стоматологических заболеваний посвящены, в основном, связи группы крови АВ0 со здоровьем пародонта. Существуют исследования, изучающие распространённость кариеса у людей с разными группами крови. Мы проанализировали более 100 статей, индексированных в RSCI, PubMed и Scopus, в основном за последние 10 лет. Для статьи было использовано 48 источников, из которых 16 опубликованы за последние 5 лет. Работы, опубликованные ранее 2005 года, из анализа исключались.

Ключевые слова: группы крови, антигены системы АВ0, предрасположенность к заболеваниям, инфекционные, соматические и стоматологические заболевания, кровь

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INTRODUCTION

Currently, the problem of early diagnosis and detection of predictors of pathological conditions and diseases of various etiologies is acute. Paradoxically, blood type can act as such a predictor. The search for a relationship between blood type and predisposition to certain diseases has been going on for several decades, but the question remains open. The solution to this issue will make it possible to identify risk groups and develop preventive measures for certain diseases, since almost everyone undergoes a routine blood type examination according to the ABO system and the Rh factor. Blood system antigens are an important individual, species, and population characteristic, reflecting the diversity and peculiarities of maintaining the body's homeostasis [1]. The antigens of the ABO blood group system, discovered by K. Landsteiner, are expressed not only on erythrocytes, but also on leukocytes, platelets, epithelial and endothelial cells, and various types of neurons [2], which makes it legitimate right to use the term histo-blood group, emphasizing the systemic nature of the response. Presently, the relationship between infectious and non-communicable diseases and blood type is being discussed not only according to the ABO system [3-6], but also according to Rhesus, Lewis and others systems [3, 6]. However, despite the fact that there are many studies [7-10] that show statistical correlations between blood groups and certain diseases, there is currently no consensus on the exact mechanisms of this association.

More than 100 articles indexed in RSCI, PubMed, and Scopus were analyzed, mainly over the past 10 years. A total of 48 references were utilized in this study, among which 16 were published within the last five years. Any works published prior to 2005 were excluded from the analysis.

THE AIM

To analyze modern scientific literature containing theories and studies that explain the mechanisms of conjugation between different blood groups and predisposition to certain diseases.

Oncological diseases

The interrelation of blood type and cancer is the most studied [3, 4, 11, 12]; mechanisms for the implementation of such interrelation are proposed. Studies conducted in the 1950s have shown that risk of stomach cancer development is about 20 % higher [4, 5, 12, 13] in people with blood type II (A) compared to people with blood type I (O). People with blood type IV (AB) are more susceptible to this disease [4, 13]. It has been proven [5] that the antigen A presence in people of blood groups II and IV negatively affects the production of hydrochloric acid, which reduces antibacterial protection. In this regard, individuals with blood type II(A) possess significantly increased rates of *H. pylori* infection than those without this antigen. It is known that *H. pylori* is one of the numerous factors

which can cause metaplasia of the gastric epithelium [4, 5]. Also, the individuals with blood groups II (A) and IV(AB) have a decrease in the production of intercellular adhesion molecule type 1, which reduces antitumor immunity [3]. However, these are not the only factors contributing to the high incidence of cancer in people of blood type II (A).

The antigens of the ABO and H-antigen systems have a leading role in oncogenesis, metastasis, prognosis of the tumor process [4, 5]. They can be observed in epitheliocytes of the digestive system, respiratory, urinary and reproductive systems [2, 5]. Tumor cells, especially of epithelial origin, can also express antigen A or a similar antigen. With malignancy of the tumor, the number of such antigens decreases or absent at all. This happens because the transcription of A-transferase is suppressed due to DNA methylation in the region of the gene responsible for the expression of antigen A. The smaller the antigen, the greater the malignancy of the tumor. The loss of antigens A and, to a lesser extent, the loss of antigen B are proportional to the metastatic potential of the tumor [5], because a lack of these antigens blocks the immune antitumor response. Those tumors where A or A-like antigens are present will be perceived as alien and interact with antibodies, which will lead to an attack on tumor tissue.

Individuals with blood type II(A) do not have an immune reaction to the A-antigen. Therefore, malignant cells with the A-antigen or similar antigens will not be recognized as allogenic, so such cells will not be destroyed by the immune system. Thus, the absence of antigen A in people with blood group I(O) can be considered as a factor of antitumor protection against epithelial malignancies, such as cancer of the reproductive system in men and for women, intestinal cancer, pancreatic cancer, which is also more common in people without I(O) blood group [4, 5, 6].

Also, the normal expression (Fig. 1) of antigens A, B or H [14] changes in patients with lymphoma or leukemia.

Modern literature addresses two mechanisms through which these antigens are lost (Fig. 2) [4]. The first mechanism is due to the chromosomal translocation of the region of chromosome 9 responsible for information about A- or B-transferases. The activity of A- and B-transferases, individually or both at the same time, is inhibited, which leads to an increase in antigen H, which is no longer transformed into antigens A and B. Breakdown can also occur

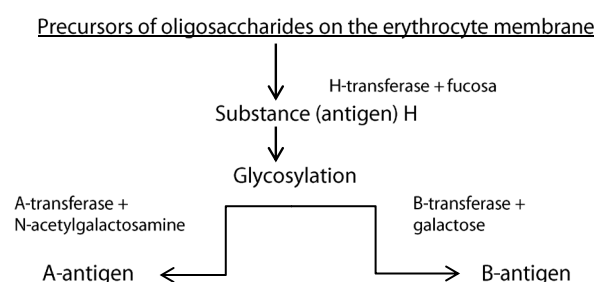


FIG. 1.
Formation of A, B and H antigens on human erythrocytes

at the level of formation of H-antigen, as a precursor of antigens A and B (the second possible mechanism). For example, by reducing the amount or activity of H-transferase. Thus, the suppression of the expression of A- and B-antigens can be considered as a predictor of malignant diseases of the blood system and act as a factor that allows assessing the dynamics of the disease. It has been shown that normal expression of antigens A and B by blood cells occurs during remission. With the recurrence of leukemia or lymphoma, such expression decreases or cells that have lost A- and B-antigen reappear [4].

At the same time, the predominance of blood group II (A) was not revealed in patients with brain tumors [9], a slight predominance of III(B) was found, which the authors of the study explained by the relative isolation of the tumor from the general immune system. In tumors, there is not only a connection with the AB0 antigen system, but also with the Lewis system [4, 5]. The antigen Le^b is an antigen associated with colon adenocarcinoma, and the Lewis system antigens (Le^a and Le^b) are co-expressed in tumor tissue. Therefore, the relationship of blood type with predisposition to certain oncological diseases can be considered proven. However, the variability of the localization of tumor growth and their diversity provide a wide field for discussion.

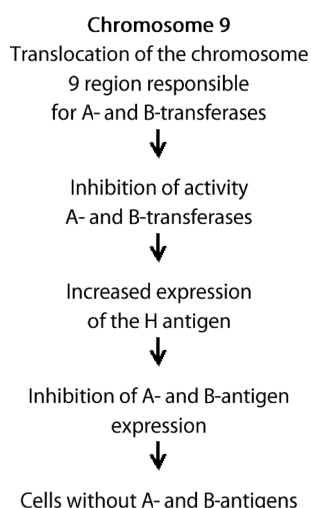
Metabolic disorders. Hyperlipidemia

People with blood type II(A) have decreased serum levels of apo-lipoprotein B-48, which is involved in the formation of chylomicrons [5, 15]. This may be due to the genetically determined low activity of intestinal alkaline phosphatase (I-ALP). It is believed that this enzyme is essential for the crossing of chylomicrons from the intestine into the blood. Due to this, representatives of the II(A) blood group have a lower level of cholesterol in the blood serum than those of the owners of other groups. However, that data need to be clarified due to the fact that the inheritance of metabolic disorders is multi-factor and is not managed by a single gene. Some studies have shown that blood groups II(A) and III(B) contain lower levels of HDL and higher levels of LDL, total cholesterol and triglycerides. The blood group IV(AB) protected against hyperlipidemia [16].

Diabetes mellitus (Type 2 diabetes)

There is currently no clear association of the risk of developing type 2 diabetes mellitus (DM2) with the blood type [5, 16]. According to a study by Fagherazzi G. et al., there is no connection between the Rh blood type and the possible development of DM2 [5]. According to the AB0 system, people with blood type I(0) have the lowest risk of developing DM2 [17-19], and those with blood type III(B) have the highest risk [20, 21]. A possible protective effect in individuals with blood type I(0) is associated with the lack of activity (or low activity) of transferases, namely glycosyltransferase [14]. It is known that in the presence of active glycosyltransferase, the level of inflammatory mediators is higher [21]. This leads to the development of immune and inflammatory reactions, which play a significant role in the development of DM2. When assessing blood groups according to the Rhesus and AB0 system, the highest risk

First mechanism of antigen loss



Second mechanism of antigen loss

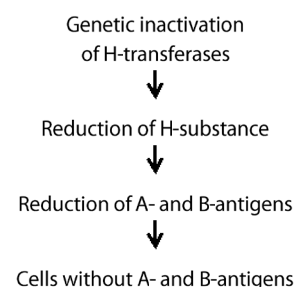


FIG. 2.

Mechanisms of antigen loss at malignant diseases of the blood system

was also found in people with blood group III(B) Rh+ [5, 20]. Nevertheless, research undertaken in different nations has not demonstrated a similar correlation.[20, 21]. Perhaps the metabolic status [1, 22] (lipid profile, fasting glucose level, etc.) is important, influencing the implementation of the mechanisms of diabetes mellitus development.

Psychological status and nervous system disorders

The relationship of blood type is discussed not only with certain diseases, but also with typological personality traits, temperaments, and response to stressful factors [23-26], which in turn may predispose to the development of not only somatic, but also mental illnesses [3]. One of the first theories of the conjugation of blood type and psychological status was proposed in the 30s of the last century by T. Furakawa [25], and discussions on this issue continue to this day. For example, there have been attempts to link blood type and aggression (external (verbal and physical) or internal (negativism, resentment, guilt)) [23]. Representatives of blood groups I(0) and II(A) had a tendency to direct aggression directed at another person, while representatives of blood groups III(B) and IV(AB) had more frequent manifestations of internal aggression. These studies are based on the assumption that blood type is a marker of biochemical individuality [23, 24], which can manifest itself in behavioral reactions. The authors propose that the schematic representation outlined is essential to understanding the interplay between blood type and the body's inclination towards specific ratios of hormones and neurotransmitters, including cortisol, catecholamines, dopamine, and gamma-aminobutyric acid (GABA), which subsequently influence behavioral outcomes. Nevertheless, such conclusions also have an ethical aspect. Historically experience shows that attempts to find "ideal" biological markers (including racial theories) have led to scientifically unsound conclusions.

This warns against similar simplistic interpretations of blood type data.

Individuals with blood type IV(AB) have a higher risk of stroke and cognitive impairment [5, 11, 27, 28] in both men and women. Such cognitive impairments can occur not only as a result of stroke, but also in its absence, for example, due to neurodegenerative diseases [27]. A higher risk of stroke and cognitive impairment was noted in the carriers of blood group IV(AB) in all age groups [5, 27]. Similarly, the proportion of mental disorders in people with blood type IV(AB) is almost 3 times higher than the average in the population [25]. This could be attributed, among other factors, to psychological traits, the degree of synthesis, and the balance of neurotransmitters previously discussed. Although research data are contradictory [27], most of them indicate that people with blood type IV(AB) are more likely to have Alzheimer's disease [5]. Alzheimer's disease is based on pathological activity and impaired elimination of beta-amyloid and tau proteins, which have a toxic effect on brain tissue and disrupt the formation of neuronal connections. One of the reasons leading to a violation of the elimination of pathological proteins is genetic. It can be assumed that inherited biochemical features associated with blood type can influence the pathogenesis of neurodegenerative diseases.

Research indicates that individuals with the I(0) blood group, as classified by the ABO blood group system, tend to possess a significantly greater volume of gray matter in the brain when compared to other blood groups [27]. Perhaps this is a shielding factor against neurodegenerative diseases, including Alzheimer's disease, in which number of neurons of the brain progressively decreases. The protective role of blood group I(0) in the aging of not only the brain, but also the body as a whole is discussed [29, 30]. This may be due to the fact that the plasma levels of von Willebrand factor (vWF) and factor VIII (FVIII) are lower in people with the first blood group than in people with other blood groups [27, 31, 32]. It may reduce risks of thrombosis in development of vascular pathologies during aging.

Infectious diseases

Researches have shown [6] that blood group I(0) has a high resistance to most infectious agents compared to other blood groups. However, when exposed to *Mycobacterium tuberculosis*, vibrio cholera, or *Yersinia pestis*, the risk of infection in people with blood type I(0) is quite high [3]. They are more likely to have a severe, progressive course of these infections. The antigens of some bacteria are similar to those of blood groups, and this largely determines the immune response to these antigens [14]. Thus, people with blood group III(B) are more likely than those with groups I(0) and II(A) to have an infectious process caused by *E. coli*, since the B antigen is similar to the antigen of the microorganism, therefore, the immune response does not develop or is insufficient. For the same reason, people with blood type IV(AB) have a high probability of escherichiosis. Statistically, the carriers of this group are more likely to have severe forms of smallpox and salmonellosis, and people with blood type II(A), in addition

to smallpox, often have an infection caused by *Pseudomonas aeruginosa* [3, 6]. Probably it is due to the affinity of pathogens to blood group antigens [3], which are expressed not only on erythrocytes, but as well as on epithelial cells. There is a version that the prevalence of a certain blood type in a given territory is largely due to natural selection due to epidemics raging in a particular region or country. For example, the inhabitants of West Africa have practically no Duffy antigen, which was the result of selection providing protection against *Plasmodium vivax* [6]. However, the variety of strains of viruses and bacteria, as well as the variety of adhesives used by them, does not allow us to make an unambiguous conclusion about the connection of a blood group with a particular disease. Rather, it is worth talking about the tropicity of a particular pathogen to a certain antigen that determines the blood group.

In recent years, the relevance between blood type ABO, Rh factor and susceptibility to coronavirus infection (COVID-19) has been studied [33-36]. It was found that blood group II(A) is associated with an increased infection risk, severe and even fatal course of the disease, while those with group I(0) are characterized by resistance of the bronchopulmonary system to coronavirus or, in the presence of infection, relatively mild course of the disease. It is assumed that the SARS-CoV-2 virus is able to bind directly to antigen A, which is located on epithelial cells of the respiratory tract, which increases the viral load [8]. In addition, individuals with blood type II(A) have not natural immunity to polysaccharides A, which leads to a lack of immune response and a more severe course of infection. Individuals with blood type II(A) have a higher level of von Willebrand factor [5, 31, 33], which is a possible cause of thrombotic complications.

Dental diseases

Studies of the blood groups influence on predisposition to the dental diseases development are largely devoted to the relationship between the blood group and periodontal health [37-39]. However, the results of the observations vary significantly. For example, a study of the results of the D. Mostafa research [37], which evaluated the condition of 1126 patients with chronic periodontitis, revealed an increased risk of developing an inflammatory process in periodontitis in people with blood type I(0). A possible mechanism explaining this phenomenon is a reduced level of IgA in the oral fluid in patients with blood type I(0), which makes the anti-infective protection of the oral cavity vulnerable. On the contrary, Gurpur Prakash Pai and co-authors [38] noted the highest percentage of people with healthy periodontitis among the owners of blood group I(0). At the same time, gingivitis and periodontitis in their work were more often diagnosed in subjects with A(II) and B(III) blood groups [38]. This is probably due to the fact that antigens A and B, which are also present on mucosal epithelial cells, act as receptors for the fixation of tropic bacteria.

According to other data [39], the 61-kDa bacterial adhesive protein is considered as a tropic for the H antigen, which is a precursor of the B and A antigens. The expression

of the H antigen precursor is carried out mainly by cerebrospinal cells; however, it can also occur in non-keratinized epithelium, including the epithelium of the oral mucosa. Individuals with blood type I(0) have the highest amount of H antigen, including in the gum tissues, which, according to researchers, may contribute to the attachment of gram-negative bacteria and a greater risk of developing an inflammatory process [39].

There are studies examining the prevalence of caries in people with different blood types [40, 41, 42]. It has been established that individuals with different blood groups have different saliva composition parameters; therefore, their resistance to various infectious agents differs, which affects the development of caries [41, 42]. According to studies, the incidence of caries was statistically higher among people with blood type III(B) ($p < 0.05$) [41] and with Rh-positive blood type IV(AB) [42].

Some studies assessing the risks of developing various types of cancer of the oropharyngeal region also suggest taking into account the phenotype of the patient's blood [43, 44]. Since blood antigens A/B, precursors, or related antigens (H, Lewis, li) are expressed in endodermal epithelial cells, where most cancers occur, the blood group can detect tumor-related glycosylation changes. There is evidence of the relationship between blood type and the propensity to develop oral potentially malignant disorder [45]. It was revealed that people with blood type "B" were 1.46 times more susceptible to acquiring oral potentially malignant disorder, such as leukoplakia and lichen planus [45]. The authors suggest that blood group antigens on the cell surface play a role in protecting mucous membranes, and suggest informing people with blood group B who have bad habits that they are more likely to develop oral potentially malignant disorder.

Other somatic diseases

Blood type III(B) is a predictor of severe rheumatoid disease due to the higher frequency of the haptoglobin 2-2 phenotype [46], which predisposes to a clinical variant with a tendency to frequent and prolonged exacerbation. Belonging to blood group III(B) is associated with a higher risk of arterial hypertension compared to other blood groups according to the ABO system [7, 16].

The relationship between the ABO blood group system and coagulation abnormalities is associated with the function of von Willebrand factor (vWF), which serves as the transport protein for factor VIII (FVIII) [11, 28, 31, 32, 47]. Von Willebrand factor participates in both primary (vascular-platelet) and secondary (coagulation) hemostasis. A decrease in its quantity and activity is accompanied by a risk of bleeding (persons with blood type I(0)) [11, 31]. This risk must be taken into account when performing surgical interventions, especially long-term ones, such as joint replacement. Similarly, in people with blood type I(0), a decrease in prothrombin (FII) and proconvertin (FVII) levels was noted, which indicates the peculiarity of both the external and internal pathways of coagulation hemostasis in these subjects [31]. A decrease in the level of coagulation factors contributes to the development of bleeding, but at the same

time protects against excessive thrombosis, which occurs in atherosclerosis, coronary heart disease, thrombophlebitis, etc. [27, 48]. Increased activity of the coagulation system is of great importance in the pathogenesis of heart attacks and other "vascular" disasters. The H-antigen present on erythrocytes of group I(0) affects the metabolism and duration of action of vWF, shortening the time of its activity [31]. A longer half-life, therefore, a higher concentration of vWF and the coagulation factor FVIII carried by it in the blood plasma of other groups, especially II(A), lead to an increased likelihood of thrombosis and thromboembolism. However, according to a study by O.A. Gusyakova, et al. [31], in individuals with blood type II(A), there is a compensatory increase in the activity of anticoagulant and fibrinolytic systems, which prevent the development of thrombosis for a long time.

The development of cardiovascular diseases (coronary heart disease, arterial hypertension, etc.) is facilitated by the influence of blood group antigens on erythrocyte aggregation [7]. An increase in the ability to aggregate leads to an increase in blood viscosity, increased peripheral resistance to blood flow and the risk of thrombosis. The negative charge of the erythrocyte membrane, which also depends on the expressed antigens, enhances their mutual repulsion and increases resistance to aggregation. Individuals with blood type I(0) who have a "basic" antigen have a lower risk of cardiovascular pathologies [7]. There is also evidence that the genes that determine the ABO blood type are associated with the genes responsible for the expression of tumor necrosis factor (TNF), which has a significant effect on endothelial function, capillary permeability and coagulation [7].

CONCLUSION

The review does not include all diseases and conditions in which there is a link between them and blood type. The association of blood type with the development of schizophrenia [3], HIV infection [6] and others is discussed [1, 5, 11]. Modern research suggests mechanisms for this coupling, but existing theories and proposed mechanisms need to be clarified. Blood group antigens are important genetic and immunological factors that affect the level of pro-inflammatory and anti-inflammatory agents, the state of the coagulation and anticoagulation systems, and response characteristics. The review can help in the development of screening programs and the individualization of preventive measures. For example, people with blood type 1 who are predisposed to bleeding may be advised to conduct an in-depth study of coagulation hemostasis before surgery. For people with blood groups 2 and 4 with an increased risk of developing stomach cancer, it is advisable to undergo a medical examination with the mandatory inclusion of fibrogastroduodenoscopy in the study plan. For people with blood type 3, especially Rh-positive ones, it is possible to include earlier monitoring of blood pressure and glycemia in the examination plan. Further research

to establish the mechanisms of the relationship between blood type and pathological conditions will shed light on many links in the pathogenesis of various diseases. Blood group antigens may become markers of the pre-nological diagnosis of certain conditions [4, 10, 19, 22], that makes it advisable to include the blood type in predictive diagnostic algorithms. This will make it possible to develop preventive measures and carry out early diagnosis of many diseases.

Conflict of interest

The authors declare that they have no competing interests.

Author's contributions

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