Chapter

ABO Blood Groups and Risk of Glioma

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Abstract

Gliomas are one of the most common primary brain tumors and the etiology of gliomas remains unknown in most cases. The aim of this case–control study was to investigate possible association between incidence in relation to glioma and certain blood groups. This study included 100 histopathologically verified cases of glioma and 200 age and sex-matched controls without malignant diseases that were admitted to the same hospital. The results revealed that the patients with group AB were at 3.5-fold increased risk of developing glioma compared to the patients with other ABO blood groups. In this particular study, there was more male patients with glioma with the blood group AB. However, mechanisms that explain the relationship between the blood groups ABO and a cancer risk are unclear. Several hypotheses have been proposed, including the one with a modulatory role of blood group ABO antigens. In addition, the blood group ABO system regulates the level of circulating proinflammatory and adhesion molecules which play a significant role in the tumorigenesis process. Additionally, the recent discovery that includes the von Willebrand factor (vWF) as an important modulator of angiogenesis and apoptosis provides one plausible explanation as regards the role of the blood group ABO in the tumorigenesis process. To our knowledge, this is the first study that examined the relationship of blood group in patients diagnosed with glioma among the Serbian population. Moreover, for the first time our study results suggested that blood group AB increased the risk of glioma. The results of this study suggested that the blood group AB could be one of hereditary factors which had an influence on the occurrence of glioma. The further research is needed on a larger sample, to confirm these findings and the possible mechanisms by which the ABO system contributes to the pathology of glioma.

Keywords: ABO blood groups, risk factors, glioma

1. Introduction

The three most prevalent primary tumors of the brain, which represent the most common neoplasm of all brain tumors, are glioma, meningioma and pituitary adenoma. The most common primary brain tumors are gliomas [1]. Gliomas account for 27% of all central nervous system tumors and about 80% of malignant brain tumors. Based on the histological criteria, gliomas are classified into the following subtypes: astrocytoma, glioblastoma, oligodendroglioma, ependymoma, mixed glioma, malignant glioma, not otherwise specified (NOS) and a few rare histologies [2]. Each year, approximately 100,000 people are diagnosed with glioma worldwide. In addition, gliomas comprise less than 2% of all newly diagnosed cancers

and are associated with substantial mortality and morbidity [3]. Glioblastoma multiforme (GBM) is the highest grade glioma (grade IV) tumor according to the grading system of the World Health Organization (WHO classification), and accounts for more than 50% of all gliomas [4]. The median overall survival of patients with glioma is approximately 14-17 months, whereas the incidence of gliomas is 6.8/100,000 and it is increasing worldwide. The countries with Northern European populations had higher incidence rates (ranging from 7.8 in the USA to 9.6 in Australia and New Zealand). However, a decline in the incidence rates was noticed in countries with predominantly Asian and Africans populations (ranging from 1.9 in Southeast Asia to 3.3 in India) [5]. Considering the fact that the etiology of glioma is largely unknown, numerous risk factors have been examined as potential contributors to glioma risk. As a result, several potential factors are found to be increasing the risk of developing glioma and they included environmental factors such as smoking, alcohol consumption, diet, obesity, infections, environmental pollution, and ionizing radiation [6, 7]. In this regard, some epidemiological studies suggested that allergic conditions (such as asthma, hay fever, eczema, food allergies, etc.) reduced the risk of glioma [8]. Well-established risk factors for glioma development include older age, male gender, Caucasian race/ethnicity, complete with rare genetic syndromes. Li-Fraumeni syndrome, neurofibromatosis (types 1 and 2), tuberous sclerosis, nevoid basal cell carcinoma syndrome, familial adenomatous polyposis (FAP), and von Hippel–Lindau (VHL) syndrome cause a small percentage of gliomas in adult populations [9–11]. In addition, ABO blood groups, expressed by different cells in human tissues, including epithelial cells, vascular endothelial cells, and neurons [12], have been associated with an increased cancer risk.

Many recent studies have focused on the role of ABO blood group antigens in the pathogenesis of various systemic diseases, including cancer. Recently, more evidence suggested that there was a significant association between the distribution of ABO blood group antigens and a risk of tumors, including the development of pancreatic cancer, hepatocellular carcinoma, nasopharyngeal carcinoma, and gastric cancer [13–15].

Furthermore, several studies have shown conflicting results concerning the relationship between ABO blood groups and glioma risk [16–29]. Finally, differences are observed not only in the distribution of ABO blood group antigens among patients with primary brain tumors in various countries worldwide, but also among different ethnic groups within the country. The influence of blood group types on the pathogenesis of brain tumors is still unclear, considering the fact that there are conflicting reports obtained from the studies related to the distribution of ABO blood groups and a risk of developing glioma.

2. The relationship between ABO blood group and cancer risk

The ABO blood group system was discovered at the University of Vienna in 1901 by Austrian scientist, Karl Landsteiner. The locus for the ABO blood group is on chromosome 9, whereas ABO gene is inherited in an autosomal dominant [30]. The A and B antigens are displayed on the surface membrane of red blood cells and attached to a common precursor of the side chain, the H determinant, which is then converted into the A or B antigen. As regards the expression of antigens, individuals with blood type AB have both antigens (A, B). On the other hand, individuals with blood type A have antigen A, individuals with blood type B have antigen B, whereas individuals with blood type O have neither antigen A, nor antigen B. Moreover, the individuals of group O lack such functional enzymes and express the unaltered H

determinants. In addition to their expression on the erythrocytes, A and B antigens are highly expressed on the surface of epithelial cells of gastrointestinal, bronchopulmonary, and urogenital tracts. Ultimately, they are expressed on the surface of the neurons, platelets, and vascular endothelium [31, 32].

The possibility of association between ABO blood type and malignancy was first explored by Anderson and Haas. ABO blood group antigens are widely expressed in a variety of human cells and tissues. As previously mentioned, the underlying mechanisms that could explain the direct relationship between the ABO blood groups and cancer risk still remains a challenge. One of the probable explanations refers to the modulatory role of ABO blood group antigens. In addition, a variety of tumors show modified expression of ABO antigens on the surface of cancer cells in comparison with normal epithelial cells [32–34]. Moreover, what may prevent the immune system from recognizing and destroying tumor cells is the structural similarity observed between ABO blood groups antigens and tumor antigens. That results in a greater risk of cancer development and progression [35]. In particular, glycoconjugates are considered to be the key mediators of membrane **signaling** and intracellular adhesion. Hence, they are necessary for malignant progression and metastasis [36]. In addition, a link was detected between ABO gene polymorphism and proinflammatory and adhesion molecules (such as E-selectin, P-selectin, and intracellular adhesion molecule-1) which play an important role in tumorigenesis. It is well known that low levels of intercellular adhesion molecule –1 (ICAM-1) facilitate the adhesion of some cancer cells to endothelial cells in patients with a non-O blood group. Furthermore, low-level ICAM-1 may accelerate cancer progression [37].

Taking into account that the Von Willebrand factor (vWF) plays an indirect role in the tumorigenesis process, it has to be emphasized that its main function is to initiate platelet adhesion to the endothelial cells upon vascular injury. Being an important modulator of angiogenesis and apoptosis, vWF is secreted by vascular endothelial cells. The lowest serum levels of these factors have been associated with the O blood group, the intermediate levels – with blood groups A and B, whereas the highest levels have been associated with blood group AB. In this manner, we did observe a positive correlation between levels of vWF and disease severity. The level of vWF is an indicator of the extent of endothelial dysfunction caused by tumor growth. Thus, elevations in the concentrations of plasma vWF could be related to accelerated tumor growth in individuals with non-O blood groups [38, 39]. As regards the Forssman antigen (FORS1 Ag), which is structurally similar to the structure of A antigen determinant of the ABO blood group system, it is synthesized predominantly in stomach and colon cancer. However, one study confirmed the presence of Forssman antigen in hepatocellular carcinoma tissues [40]. Alterations in surface antigens, particularly glycoconjugates, may not only lead to modifications in intercellular adhesion, but could have an important role in the development of cancer as well. There is still no formal hypothesis which would provide a plausible explanation about the association between malignancy and ABO blood groups [35]. Consequently, the ABO gene may be in linkage disequilibrium with other genes influencing cancer risk [41].

2.1 The relationship between ABO blood groups and risk of pancreatic cancer

The results obtained from three previously conducted studies indicated a lower incidence of pancreatic cancer among people with blood group O. Additionally, the Nurses' Health Study and the Health Professionals Follow-Up Study demonstrated an increased incidence of pancreatic cancer among subjects with blood type antigen A or B compared with those who were lack of these antigens [42–44].

Dandona et al., also observed an increased risk of developing pancreatic cancer in patients with a non-O blood group [45].

2.2 The relationship between ABO blood group and risk of gastric cancer

Based on the results of previously conducted study, which included 3,623 patients from England and Scotland, a significantly higher frequency of the A blood group and a lower frequency of the O blood group was observed among stomach cancer patients. In addition to the above mentioned findings, it was also revealed that the people with blood group B showed a significantly reduced risk of stomach cancer [46]. On the other hand, several studies, mostly conducted in Western populations, consistently showed an approximately 20% excess risk of gastric cancer in individuals with blood type A [47]. The results obtained from this particular study confirmed in a recent meta-analysis [48]. Furthermore, there was a prospective cohort study in a Taiwanese population that showed the fact that blood type A was associated with a 38% increased risk of stomach cancer [49]. In addition, another prospective cohort study that included middle-aged or older Chinese men demonstrated a lower risk of all cancer for blood type B, as well as a lower risk for gastrointestinal cancers including stomach and colorectal cancer for blood types B and AB rather than blood type A [50]. In a study by Aird et al., no association was found between the ABO blood group and risk of stomach cancer [51].

2.3 The relationship between ABO blood groups and lung cancer

The increased risk of developing lung cancer was observed in patients with non-O blood type in Turkish populations [52].

2.4 The relationship between ABO blood groups and breast cancer

Having studied the association between ABO blood groups and breast cancer, Stamatokos et al., suggested that an A antigen was associated with an increased risk of developing breast cancer. In contrast, Tryggvadottir and colleagues observed an increased risk among women with B antigen [53, 54]. On the basis of the results of a meta-analysis, it was concluded that blood group A was positively linked with an increased risk of breast cancer [55].

2.5 The relationship between ABO blood groups and colon cancer

According to the findings of a meta-analysis, which evaluated the association between the ABO blood group and colon cancer, the protective effects of O blood type were confirmed. However, blood types A and B were not linked to a higher risk of colon cancer [56].

2.6 The influence of ABO blood group on the development of glioma

The Central Nervous System (CNS) lesions are known to mankind since 1774. Systemic study of the CNS commenced when Baily and Cushing started their studies in the early 1920s [57]. The association between brain tumors and blood groups antigens is variable. No specific hypothesis has been proposed for the association between CNS neoplasms and ABO blood groups. The abovementioned mechanisms may operate even in the CNS neoplasms. Kumarguru et al., suggested a probable hypothesis which was related to the fact that an alteration in the characteristics of ABO blood group antigens on the surface of cell origin, under the

influence of either environmental factors or genetic factors, may govern the process of development of tumors. In this regard, the mechanism may operate not only in the primary neoplastic lesions but in the metastatic lesions of the CNS in the genetically susceptible individuals as well [58]. Taking into account that there are conflicting reports obtained from studies done on the distribution of ABO blood groups in primary intracranial neoplasms, the influence of blood group types on the pathogenesis of brain tumors still remains unclear. Periayavan S et al., observed that blood group O was common in most of the categories of CNS lesions: neuroepithelial tumors (38.45%), meningeal (37.57%), cranial and paraspinal nerve tumors (39.67%), pituitary neoplasms (43.62%), and metastatic tumors (43.18%) [59]. As regards the study undertaken by Mehrazin M et al., neuroepithelial tumors (38.4%), cranial and paraspinal nerve tumors (35.9%), and pituitary neoplasms (4.40%) were observed more frequently in O blood group patients in their study [59]. In contrast, previous studies showed different results concerning the ratios of blood groups among the patients with glioma. Yates and Pearce conducted the first study which examined the relationship between the ABO blood group and the risk of glioma [16]. In this respect, there was no significant relationship found between ABO blood groups and risk of glioma among patients diagnosed before 1945. After that year, a highly statistically significant decrease in number of patients with blood group O was reported. The relationship between the blood groups and astrocytic brain tumors was examined in the study conducted by Selvestrone and Cooper [17], the results of which showed a statistically significant decrease in the number of patients with blood group B and O. In addition to the abovementioned studies, in an Italian case–control study that recruited 195 cases of histologically-confirmed glioma, a positive association was found with blood group A when low-grade astrocytomas were considered separately. Additionally, the present study identified suggestive, but non-statistically significant association with the presence of CNS tumors among the first and second-degree relatives [18]. Compared to the general population, Campbell et al., reported a substantially higher incidence of glioma in blood group O individuals [19]. Yates et al., did not detect any significant differences in the distribution of blood group antigens between glioma patients and controls from the Oxford region in the United Kingdom [20]. These results were confirmed by Strang et al., in a study that included 900 astrocytoma patients and the control population [21]. Furthermore, there was a significantly higher number of male cerebral astrocytoma patients with group A confirmed in this particular study.

The retrospective study conducted by Mehrazin et al., was made on 907 histologically confirmed cases of glioma and the same number of age and sex-matched controls. The distribution of ABO blood groups in this study population was compared with that of the general population. Finally, the results showed no significant differences between types of intracranial tumors and frequencies of four blood groups [22]. The case–control study by Akhtar et al., on 112 central nervous system tumors, found a significantly higher association of these tumors with blood group B patients [23]. On the contrary, in a case–control study, Akca et al., aimed to compare the patients with glioblastoma multiforme with control groups regarding ABO blood groups. On the basis of the study results, no significant differences among O, A, B and AB blood groups were shown [24]. In a study conducted by Turowski and Czochra, the analysis was based on the distribution of ABO blood groups in 271 patients treated for glioblastoma multiforme (GBM), whereas the control group included 500 patents with craniocerebral trauma. Hence, a statistically significant difference was found in the distribution of ABO blood groups between these patient groups. Moreover, higher frequency of group A and lower frequency of group O was detected in GMB patients [25]. In the cohort study, Allouh et al., included

115 patients who were diagnosed with glioblastoma multiforme (GB) in Jordan, between 2004 and 2015. Inclusion criteria were histologically confirmed glioma. Due to hospital records, data related to patients' characteristics (such as the following: age, sex, ABO blood groups, and Rh factor) were collected. Consequently, the study results suggested that individuals with group A had a higher than expected chance of developing glioblastoma multiforme, while individuals with group O had a lower chance. In addition, a lower incidence of glioblastoma multiforme was reported in individuals with group O compared to healthy blood donors and age- and sex-matched control subjects [26]. The case–control study in the Serbian population, which consisted of 100 pathohistologically confirmed glioma and 200 age and sex-matched control individuals, observed a higher incidence of glioma in patients with the blood group AB [27].

The aim of the retrospective study done by Chang et al., was to examine the relationship between ABO blood groups and brain tumors in the Chinese population. This study included 2077 cases with histologically confirmed glioma admitted at the hospital in the period between 2001 and 2016, whereas the control group included 2716 noncancer patients admitted to the same hospital. Consequently, the results showed that blood types B and AB were significantly linked to the risk of glioma [28]. In a prospective study, involving more than 100,000 adults in the United States and nearly 20 years of follow-up, no statistically significant differences in risk of glioma were identified by ABO blood type. Hence, the abovementioned study suggested that ABO blood group may not play a role in the development of glioma [29].

3. Prognostic value of ABO blood groups in patients with glioma

Some studies investigated the prognostic value of ABO blood groups in patients with glioma. Alkan et al., performed a retrospective cross-sectional study which included 759 patients with glioma. In this study, there was no statistically significant difference observed between glioma patients and healthy control patients. Median overall survival (mOS) of GBM patients were 12.9 months in A, 13.4 months in B, 5.7 months in AB, 12.8 months in 0 blood groups. The median overall survival of anaplastic astrocytoma patients were 24.4 months in A, 47.2 months in B, 37.8 months in AB, 29.2 months in 0 blood groups respectively. Therefore, these results showed that ABO blood groups had no prognostic value [60]. In a retrospective study on 72 patients with GMB, Akca et al., found no correlation among ABO blood groups and prognosis. In that study, the number of patients with blood groups O, A, B, and AB were 23, 33, 9 and 7, respectively [24]. In a retrospective observational study, Sokmen et Karcin showed that overall survival was shorter in GMB patients with non-O ABO blood groups than those with blood group O. This study consisted of 238 patients with GMB and it was the first study showing the prognostic value of ABO blood groups in patients with GMB [61]. The reason may be that the number of patients was insufficient for prognostic analyses in the study conducted by Akca et al.

The previous study, which aimed to evaluate the prognostic value in overall survival, had some limitations. With this respect, some of the studies failed to obtain data regarding O^6-methylguanine-DNA methyltransferase (MGMT) promoters, which are shown to have prognostic value in GMB. Additionally, some studies suggested that overall survival be shorter in GMB patients with non-O ABO blood groups than those with blood group O.

It is confirmed that differences in the distribution of ABO among patients with primary brain tumors have been reported between countries worldwide,

complete with differences between ethnic groups within the country which are observed as well.

As regards the effects of ABO blood groups on the incidence and survival of patients with glioma, they are still unknown. What can be confirmed is that ABO blood status has been shown to be associated with many cancers. However, the influence of blood group types on the pathogenesis of glioma is still unclear. Due to the difference of ABO genes among socioeconomic groups and geographic areas, the blood groups may have a role in the incidence and prognosis of glioma just like the environmental factors as well.

4. Conclusion

In conclusion, it should be stated that gliomas are considered to be the most common primary brain tumors, accounting for almost 80% of all malignant brain tumors. The etiology of glioma is still largely unknown. However, in the past decades, a lot of research has been focused on determining risk factors that may contribute to glioma aetiopathogenesis, including genetic and environmental factors. Previous reports demonstrated that gene mutations and ABO blood groups may be associated with elevated glioma risk. Therefore, further research of such kind is needed to be performed on a larger sample, for the purpose of confirming the abovementioned findings complete with potential mechanisms by which the ABO system contributes to the pathology of glioma.

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