ORIGINAL ARTICLES

UDC: 616.831-006:612.118
https://doi.org/10.2298/VSP161230104A

ABO blood group and risk of glioma: a case control study from Serbia

ABO krvne grupe i rizik od nastanka glioma: studija slučaj-kontrola iz Srbije

Ana Azanjac Arsić*, Svetlana Miletić Drakulić*†, Katarina Vesić*, Gordana Tončev*†

University of Kragujevac, Faculty of Medical Sciences, *Department of Neurology, Kragujevac, Serbia; Clinical Center Kragujevac, †Clinic of Neurology, Kragujevac, Serbia

Abstract

Backgraund/Aim. Gliomas are the most common primary brain tumors and the etiology is unknown. The aim of this study was to investigate possible association between incidence in relation to glioma and certain blood groups. **Methods.** The case-control study included 100 pathologically confirmed cases of glioma at the Clinical centar of Kragujevac, Serbia, between 2014 and 2015, and 200 age- and sex-matched controls without malignant diseases in personal and family history at the same institution. After signing the informed consent, all patients filled out an epidemiological questionnaire. **Results.** In the analysis comparing the glioma patients with the control group, a significant association ($p < 0.0005$) was observed in relation to the blood group AB. Furthermore, it was not observed a significant association in relation to the blood group A ($p = 0.070$), blood group B ($p = 0.256$), blood group O ($p = 0.768$) among the compared groups. Also, in the analysis comparing glioma patients with the control group, a significant association was observed in relation to the years spent in hometown ($p = 0.035$), changing the place of residence ($p = 0.007$), the body weight ($p = 0.002$) and the body mass index ($p < 0.0005$). Univariate binary logistic regression showed that higher number of years spent in the hometown [odds ratio (OR) 1.011 95% confidence interval (Cl) 1.000–1.023; $p = 0.043$], increased body weight (OR 0.976 95% Cl 0.959–0.993, $p = 0.006$) and increased body mass index (OR 0.898 95% Cl 0.839–0.961; $p = 0.002$) increase the risk of glioma. However, a change of the residence decreases the risk of glioma (OR 0.327 95% Cl 0.147–0.727; $p = 0.006$). Univariate binary logistic regression analysis revealed that the individuals with group AB were at 3.5-fold increased risk of developing glioma compared to the individuals with other ABO blood groups (OR 3,429 95% Cl 1,83–6,41; $p < 0.0005$). Also, there was more male patients with glioma with the blood group AB ($p = 0.001$). **Conclusion.** In a present study, we demonstrate that individuals with the group AB have an increased risk of developing glioma.

Key words:
glioma; blood group system; risk factors.

Apstrakt

Uvod/Cilj. Gliomi su najčešći primarni tumori mozga čija je etiologija nepoznata. Cilj ove studije bio je da ispita da li je učestalost glioma povezana sa određenom krvnom grupom. **Metode.** Studija slučaj-kontrola uključila je 100 bolesnika sa patohistološki potvrđenim gliomom u Kliničkom centru Kragujevac, u Srbiji, između 2014. i 2015. godine i 200 ispitanika kontrolne grupe ukrštenih po polu i godinama koji nisu imali istoriju malignih bolesti u ličnoj i porodičnoj anamnezi. Nakon potpisivanja pristanka svi bolesnici popunjavali su epidemiološki upitnik. **Rezultati.** U analizi, u kojoj su upoređivani bolesnici sa gliomom i ispitanici kontrolne grupe, značajna veza ($p < 0,005$) ustanovljena je za krvnu grupu AB. Nije zapažena statistički značajna veza za krvnu grupu A ($p = 0,070$), B ($p = 0,256$) i O ($p = 0,768$) između poređenih grupa. Poređenjem bolesnika sa gliomom i bolesnika kontrolne grupe, nađena je statistički značajna veza sa godinama života provedenih u mestu rođenja ($p = 0,035$), promenom mesta boravka ($p = 0,007$), telesnom masom ($p = 0,002$) i indeksom telesne mase ($p < 0,0005$). Primenom univarijantne binarne logističke regresije pokazano je da veći broj godina života provedenih u mestu rođenja [*odds ratio* (OR) 1,011 95% *confidence itnerval* (Cl) 1,000–1,023; $p = 0,043$], povećana telesna masa (OR 0,976 95% Cl 0,959– 0,993; $p = 0,006$) i povećan indeks telesne mase (OR 0.898 95% Cl 0,839–0,961) povećavaju rizik od nastanka glioma. Međutim, promena mesta boravka smanjuje rizik od nastanka glioma (OR 0,327 95% Cl 0,147–0,727; $p = 0,006$). Primenom univarijantne binarne logističke regresije otkriva se da kod osoba sa krvnom grupom AB postoji 3,5 puta veći rizik za nastanak glioma u poređenju sa osobama sa drugim krvnim grupama (OR 3,429 95% Cl 1,83–6,41, $p < 0,0005$). Takođe, bilo je više bolesnika muškog pola sa

Correspondence to: Ana Azanjac Arsić, 34 000 Kragujevac, Serbia. E-mail: ana.azanjac@yahoo.com

gliomom koji su imali krvnu grupu AB (p = 0,001). **Zaključak.** Ova studija pokazuje da kod osoba sa krvnom grupom AB postoji povećan rizik od nastanka glioma.

Ključne reči:
gliom; krvne grupe; faktori rizika.

Introduction

Gliomas are the most common primary brain tumors [1]. They accounts for approximately 27% of all brain and central nervous system tumors and about 80% of malignant brain tumors. Gliomas are tumors arising from glial or precursor cells and include astrocytoma, glioblastoma, oligodendroglioma, ependymoma, mixed glioma, malignant glioma, not otherwise specified (NOS) and few rare histologies [2].

The etiology of glioma is unknown. Several possible risk factors for glioma were suggested in the past, but with the exception of ionizing radiation, none was consistently confirmed [3, 4]. Several studies investigated the relationship between the blood groups ABO and glioma risk and demonstrated conflicting results [5–10]. The scientist Landsteiner found the blood group ABO system in 1901 at the University of Vienna. Locus ABO is localized on chromosome 9 and gene ABO is inherited in an autosomal dominant [11]. The A and B antigens are complex carbohydrate molecule and they represent extracellular domains on the surface membrane of red blood cells. The A and B alleles of the ABO locus encode different enzyme glycosyltransferases, adding N-acetylgalactosamine and D-galactose on a common precursor of the side chain, the H determinant, which is then converted into the A or B antigen. The group O individuals lack such functional enzymes, and express unchanged H determinant. In addition to the surface of red blood cells, A and B antigens are found on a variety of human cells and tissues, including epithelial cells, neurons, platelets and vascular endothelium [12, 13].

Distribution of the four different blood groups varies between countries. Generally, blood group O has highest prevalence, while blood group AB has the lowest [14]. In Serbia, the proportion of ABO blood groups is 41.5% for A, 37.5% for O, 16% for B and about 5.5% for AB [15].

The aim of this study was to examine incidence of glioma in the patients with different blood groups ABO.

Methods

The study group included a series of 100 consecutive patients (59 males, mean age 59.76 ± 10.76 years, and 41 females, mean age 58.36 ± 8.95 years) with histopathologically verified diagnosis of glioma according to the WHO criteria (ICD-O-3). Of these 100 patients, the blood groups were available in 96 patients. The study was realized according to the Declaration of Helsinki and performed in accordance with the Ethics Committee of Clinical Center Kragujevac. The criteria for inclusion into the study were the patients who had a consultative decision evaluated on the basis of stages of the disease and the general condition of the patient. Also, the criteria for inclusion into the study were primary, previously untreated glioma. The criteria for exclusion from the study were previously diagnosed and treated glioma and glioma recidivans. The patients were treated surgically, followed by radio and chemotherapy at the Center for Oncology, Clinical Center Kragujevac. Data were collected between April 2015 and May 2016. The control group included 200 patients matched by sex and age (109 males, mean age 59.32 ± 10.71 years, and 91 females, mean age 58.09 ± 9.12 years), who were hospitalized in the Clinical Centre Kragujevac, without malignant diseases in personal and family history. Of these 200 patients, the blood group were available in 172 patients. After obtaining the patient consent, a questionnaire based on the reviewed literature data and personal considerations was to collect detailed information. It included questions about different factors supposed to be a possible risk or protective factors.

The first part of the questionnaire referred to demographic features of the patients [sex, age, birth and residency places, blood type, Rh (D) antigen, school education, occupation, number of family members, the size of the home space]. The second part of the questionnaire included the family history of chronic diseases, including brain tumors and other malignant tumors. The third part of the questionnaire referred to the personal history of the disease including reproductive risk factors. The fourth part deals with information on the risks of exposure to external factors, the fifth included data on habits (smoking, drinking coffee, tea, alcohol) and the sixth part referred to information about nutrition.

Statistical analysis

Statistical analysis was performed using the SPSS software version 19.0. The chi-square (χ^2) test was used for the comparison of qualitative variables between the patients with glioma and the control group. The categorical variables were presented as frequencies and percentages. The univariate analysis using the logistic regression techniques, including the odds ratio (OR), was performed to determine the effects of blood groups on the dependent variable (glioma). The P value of less than 0.05 was considered statistically significant.

Results

Table 1 shows the demographic and personal characteristic of patients and controls. Difference in years spent in hometown between the study and the control group was statistically significant (p = 0.035). The control group patients were more frequently changing the residence than patients with glioma (p = 0.007). Also, the statistically significant difference was found between the compared groups in relation to the body weight (p = 0.002) and to the body mass index (p < 0.0005). The patients with glioma had a higher body weight and higher body mass index in comparison to the patients of the control group.

In comparing the patients with glioma with the control group patients, a significant association ($p < 0.005$) was observed in relation to the blood group AB. Furthermore, no significant association was observed in relation to the blood group A ($p = 0.070$), blood group B ($p = 0.256$), blood group O ($p = 0.768$) among the patients with glioma and the control group (Table 2).

In the group of patients with glioma, 32.3% of patients had the blood type AB, 25.0% of patients had the blood group A, 10.4% the blood group B and 32.3% the blood group O. The ratios of blood groups AB, A, B and O were 12.2% v.s. 32.6% v.s. 18.5% v.s. 34.9% in the control group, respectively (Table 2).

Comparing the male patients with glioma and the control group as the blood groups ABO, a significant association was observed in relation to the blood group AB ($p = 0.001$). There was no significant difference regarding the blood group A ($p = 0.726$), blood group B ($p = 0.668$) and the blood group O ($p = 0.726$), (Table 3).

Comparing the female patients with glioma and the control group as the blood group AB, differences did not reach significance there ($p = 0.057$). Also, there was no significant difference regarding the blood group A ($p = 0.288$), blood group B ($p = 0.549$) and the blood group O ($p = 0.522$) (Table 4).

Table 1

Demographic and personal characteristic of patients and controls

Variable	Patients with glioma (n = 100)	Control group (n = 200)	*p*
Age (years), mean ± SD			
male	59.76 ± 10.76	59.32 ± 10.71	0.779
female	58.36 ± 8.95	58.09 ± 9.12	0.876
Sex, n (%)			
male	59 (59)	109 (54.5)	0.537
female	41 (41)	91 (45.5)	0.537
Years spent in hometown, mean ± SD	47.39 ± 20.94	41.69 ± 23.45	0.035
Change of the place residence, n (%)	8 (8)	42 (21)	0.007
Birth weight (kg), mean ± SD	3.14 ± 0.57	3.63 ± 3.01	0.108
Body weight (kg), mean ± SD	82.88 ± 12.64	77.23 ± 17.04	0.002
Body height (cm), mean ± SD	172.84 ± 7.62	173.09 ± 9.65	0.813
BMI (kg/m^2), mean ± SD	27.57 ± 5.01	25.72 ± 3.30	< 0.0005
Rh factor (-), n (%)	8 (8)	25 (12.5)	0.921

BMI – body mass index; SD – standard deviation.

Table 2

Comparison of blood groups between the patients with glioma and the control group

Groups	Patients with glioma n (%)	Control group n (%)	*p*
AB	31 (32.3)	21 (12.2)	< 0.0005
A	24 (25.0)	63 (36.6)	0.070
B	10 (10.4)	28 (16.3)	0.256
O	31 (32.3)	60 (34.9)	0.768
Total	96 (100)	172 (100)	

Table 3

Distribution of blood groups in the male patients with glioma and the control group (male)

Groups	Patients with glioma n (%)	Control group n (%)	*p*
AB	18 (31.6)	8 (8.7)	0.001
A	14 (24.6)	30 (32.6)	0.726
B	7 (12.2)	17 (18.5)	0.668
O	18 (31.6)	37 (40.2)	0.726
Total	57 (100)	92 (100)	

Table 4

Distribution of blood groups in the female patients with glioma and the control group (female)

Groups	Patients with glioma n (%)	Control group n (%)	*p*
AB	13 (33.3)	13 (16.2)	0.057
A	10 (25.7)	33 (41.2)	0.288
B	3 (7.7)	11 (13.8)	0.549
O	13 (33.3)	23 (28.8)	0.522
Total	39 (100)	80 (100)	

Univariate binary logistic regression showed that higher number of years spent in the hometown (OR 1.011 95% confidence interval (Cl) 1.000–1.023; $p = 0.043$) increased the body weight (0.976 95% Cl 0.959–0.993) and increased the body mass index (OR 0.898 95% Cl 0.839–0.961) increased the risk of glioma. However, a change of the residence decreased the risk of glioma about three times (OR 0.327 95% Cl 0.147 – 0.727; $p = 0.006$) (Table 5).

The univariate binary logistic regression analysis revealed that the individuals with the group AB were at 3.5-fold increased risk of developing glioma compared to the individuals with other blood groups (OR 3.429 95% Cl 1.834–6.411; $p < 0.0005$). The blood groups A (OR 0.696 95% Cl 0.402–1.204; $p = 0.195$), B (OR 0.690 95% Cl 0.321–1.485; $p = 0.343$) and O (OR 1.064 95% Cl 0.632–1.792; $p = 0.816$) were not significantly associated with a glioma risk (Table 5).

Table 5

Univariate regression analysis of the relationship between the demographic features, ABO blood group and glioma

Variable	Odds ratio [95% confidence interval (CI)]	*p*
Age	1.004 (0.980 – 1.029)	0.728
Sex	0.832 (0.512 – 1.353)	0.495
Years spent in hometown	1.011 (1.000 – 1.023)	0.043
Change of the place residence	0.327 (0.147 – 0.727)	0.006
Birth weight	0.590 (0.317 – 1.101)	0.097
Body weight	0.976 (0.959 – 0.993)	0.006
Body height	0.997 (0.970 – 1.025)	0.826
BMI	0.898 (0.839 – 0.961)	0.002
Rh factor (-)	1.104 (0.857 – 1.423)	0.442
Blood group AB	3.429 (1.834 – 6.411)	< 0.0005
Blood group A	0.696 (0.402–1.204)	0.195
Blood group B	0.690 (0.321–1.485)	0.343
Blood group O	1.064 (0.632–1.792)	0.816

BMI – body mass index.

Discussion

In our study, we demonstrated that the distribution of blood groups in the patients with glioma differ significantly than in the control group, with a higher incidence of glioma reported in the individuals with the blood group AB. Previous studies showed different results about the ratios of blood groups in the patients with glioma**.** The study of Yates and Pearce [5], which was conducted on 473 cases with astrocytoma excluding glioblastoma multiforme, showed that in 164 patients, who were diagnosed before 1945, a distribution of the blood groups was normal. In 305 patients analyzed after that year, a statistically significantly lower number of glioma in the patients with the blood group O was noticed. Selvestrone and Cooper [6] also examined the relationship between the blood groups and astrocytic brain tumors, including glioblastoma multiforme, and they found a statistically significantly lower number of patients with the B and O blood types. The study of Jates [7] recruited 160 patients with glioma and the same number of controls and observed no significant difference in the distribution of blood groups between the glioma patients and controls from the Oxford region in the United Kingdom. Strang et al. [8] did not detect significant difference in the distribution of blood group between 900 astrocytoma patients and the control population. However, once adjusted for sex, there was significantly more male cerebral astrocytoma patients with group A ($p < 0.05$). In the meta-analysis by Zhang et al. [11] which examined the relationship between the blood groups and cancer risk were included 89 studies (82 case control studies and 7 cohort studies). The study by Akhtar et al. [9] analyzed 1674 patients with glioma and results suggested that the blood groups were not significantly associated with a glioma risk. In a recent study, Allouh et al. [12] reported a significant association between the distribution of blood group ABO antigens and glioblastoma multiforme in Jordanians, with a higher incidence reported in the persons with the blood group A.

In the last five decades, relationship between the blood groups ABO and carcinoma has been extensively investigated.

Mechanisms that explain the relationship between the blood groups ABO and a cancer risk are unclear. Several hypotheses have been proposed, including a modulatory role of blood group ABO antigens. The blood group antigens (A, B) are expressed on the surface of red blood cells and numerous other tissues. For a variety of tumor types, the blood group antigens expressed on the surface of malignant cells was found to be different from the antigens expressed on normal cells [15–17]. Modified expression of blood group antigens on the surface of cancer cells may alter cell motility, sensitivity to apoptosis and immune escape, and thus influence the initiation and spread of cancer [18]. Also, the blood group ABO system regulate the level of circulating proinflammatory and adhesion molecules (such as E-selectin, P-selectin and intracellular adhesion molecule-1), which are important for tumourigenesis. Chronic inflammation was extensively linked with a cancer development and provides a potential mechanisms by which the ABO antigens may influence a risk of cancer. One of the possible explanations about the role of the blood group ABO in the tumourigenesis process is the recent discovery of vWF that is an important modulator of angiogenesis and apoptosis. Individuals with other blood groups have significantly higher levels of plasma concentrations of vWF compared to individuals with blood group O. On the other hand, vWF may not have a significant role in cancer progression, and the elevated vWF levels can simply be an indication of the extent of endothelial dysfunction caused by tumor growth [19]. Some research have shown that the structure of certain tumor antigens is similar to the structure of antigens of the ABO blood group system. For example, Prieto and Smith [20] presented the Forssman antigen. This antigen is synthesized predominantly in stomach and colon cancer and structurally it is identical to the A antigen determinant. One study found neoexpression of ABO blood group antigens in hepatocellular carcinoma tissues. These mechanisms are biologically plausible to explain the association between the ABO blood group and a risk of cancer; the underlying mechanisms for the discrepancy among different cancer sites still remains a challenge [19].

Morever, our results suggest that a change of place of living decreases a risk of glioma and that higher number of years spent in hometown increases the risk of glioma. Until now, there have been no studies that have examined the relationship between the change of residence and a number of years spent in hometown and a risk of glioma. In this case control study, increased body weight and increased body mass index increase a risk of glioma.

Conclusion

To our knowledge, this is the first study that examined the frequency of blood group in patients with glioma among the Serbian population. Also, for the first time our study results suggest that blood group AB increases the risk of glioma.

The results of our study suggest that the blood group AB can be the one of hereditary factors which have an influence on the occurrence of glioma. The further research on a much larger sample is needed to confirm these findings as well as potential mechanisms by which the blood group ABO system affects the occurrence of glioma.

Conflict of interest

The authors report no conflict of interest.

R E F E R E N C E S

1. *Ostrom QT, Bauchet L, Davis FG, Deltour I, Fisher JL, Langer CE*, et al. The epidemiology of glioma in adults: A "state of the science" review. Neuro Oncol 2014; 16(7): 896–913.
2. *Ostrom QT, Gittleman H, Fulop J, Liu M, Blanda R, Kromer C,* et al. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012. Neuro Oncol 2015; 17 Suppl 4: iv1–iv62.
3. *Malmer B, Adatto P, Armstrong G, Barnholtz-Sloan J, Bernstein JL, Claus E*, et al. GLIOGENE an International Consortium to Understand Familial Glioma. Cancer Epidemiol Biomarkers Prev 2007; 16(9): 1730–4.
4. *Bondy ML, Scheurer ME, Malmer B, Barnholtz-Sloan JS, Davis FG, Il'yasova D,* et al. Brain tumor epidemiology: consensus from the Brain Tumor Epidemiology Consortium. Cancer 2008; 113(7 Suppl): 1953–68.
5. *Yates PO, Pearce KM*. Recent change in blood-group distribution of astrocytomas. Lancet 1960; 1(7117): 194–5.
6. *Selvestrone B, Cooper DR*. ABO blood group and astrocytomas. J Neurosurg 1961; 18: 602–4.
7. *Yates PO*. Malgnant glioma and ABO blood group. Br Med J 1964; 1(5378): 310.
8. *Strang RR, Tovi D, Lopez J*. Astrocytomas and the ABO blood groups. J Med Genet 1966; 3: 274–5.
9. *Akhtar K, Mehdi G, Sherwani R, Sofi L*. Relationship between various cancers and ABO blood groups: A Northern India experience. Int J Pathol 2010; 13(1): 1–4.
10. *Akca Z, Mutlu H, Erden A, Buyukcelik A, Sezer Y, Inal A*. The relationship between ABO blood group and glioblastoma multiforme. Med Sci 2014; 3(4): 1639–47.
11. *Zhang B, He N, Huang Y, Song F, Chen K*. ABO blood groups and risk of cancer: A systematic review and meta-analysis. Asian Pac J Cancer Prev 2014; 15(11): 4643–50.
12. *Allouh MZ, Barbarawi AM, Hiasat MY, Al-Qaralleh MA, Ababneh EI*. Glioblastoma and ABO blood groups: Further evidence of an association between the distribution of blood group antigens and brain tumours. Blood Transfus 2017; 15(6): 543–7.
13. *Landsteiner K*. Über Agglutinationserscheinungen normalen menschlichen Blutes. In: *Harper PS,* editor. Landmarks in Medical Genetics. Oxford: Oxford University Press; 1901. p. 112–4.
14. *Franchini M, Liumbruno GM*. ABO blood group: Old dogma, new perspectives. Clin Chem Lab Med 2013; 51(8): 1545–53.
15. *Liumbruno GM, Franchini M*. Beyond immunohaematology: The role of the ABO blood group in human diseases. Blood Transfus 2013; 11(4): 491–9.
16. *Hsiao L, Liu N, You S, Hwang L*. ABO blood group and the risk of cancer among middle-aged people in Taiwan. Asia Pac J Clin Oncol 2015; 11(4): e31–6.
17. *Jovanović SS, Veljković DK*. Immunobiological and clinical significance of blood groups. Beograd: Intra Net Communication; 2009. (Serbian)
18. *Louis DN, Perry A, Reifenberger G, Deimling A, Figarella-Branger D, Cavenee WK,* et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: A summary. Acta Neuropathol 2016; 131(6): 803–20.
19. *Franchini M, Lippi G*. The intriguing relationship between the ABO blood group, cardiovascular disease, and cancer. BMC Med 2015; 13: 7.
20. *Prieto PA, Smith DF*. A new ganglioside in human meconium defected by antiserum against the human milk sialylohigosaccharide 2S-tetrasaccharide b. Archives of Biochemistry and Biophysics 1985; 241(1): 281–9.

Received on December 30, 2016.
Revised on March 24, 2017.
Accepted on July 06, 2017.
Online First September, 2017.