Family history of disease and risk of glioma occurrence: Results of the case-control study

Porodična istorija bolesti i rizik od nastanka glioma: rezultati studije slučaj-kontrola

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Abstract

Background/Aim. Malignant gliomas represent a heterogenaus group of tumors. They occur in all age groups, predominatly in males in older age. The purpose of this case-control study was to examine the association between risk for developing glioma and family history of diseases. **Methods.** The case-control study included 100 pathologically confirmed cases of glioma at the Clinical Centre Kragujevac, Serbia, between 2015 and 2016, and 200 age- and sex-matched controls without glioma and other malignant diseases in personal and family history at the same institution. After signing the informed consent all the patients filled out an epidemiological questionnaire. Multivariate logistic regression analyses was used in statistical data processing. **Results.** Malignant diseases in family history were more common in the study group than in the control group [odds ratio (OR) = 1.821, 95% confidence interval (CI) 1.004–3.305; p = 0.049]. The most common malignant tumor in the study group were cancer of the uterus (7%) and colon cancer (6%), while in the control group the most common cancer were lung cancer (6%) and cancer of the uterus (7%). Diabetes mellitus in family history was more common among control individuals than among glioma patients (OR = 0.520, 95% CI = 0.271–0.995; p = 0.048). Also, our results showed that cardiovascular diseases in family history were more common in the control group than among patients of the study group (OR = 0.557, 95% CI = 0.325–0.953; p = 0.033). **Conclusion.** In this case-control study, we observed a statistically significant relation between family history of malignant diseases and glioma. Also, we found statistically significant inverse relation between family history of cardiovascular diseases and diabetes and glioma.

Key words:
glioma, family history of disease; medical history taking; epidemiology; neoplasms.

Apstrakt

Uvod/Cilj. Maligni gliomi predstavljaju heterogenu grupu tumora koji se javljaju većinom kod starijih muškaraca. Cilj ove studije bio je da ispita vezu između porodične istorije bolesti i rizika od nastanka glioma. **Metode.** Studija slučaj- kontrola uključila je 100 ispitanika sa patohistološki potvrđenim gliomom u Kliničkom centru Kragujevac, Srbija, između 2015. i 2016. godine i 200 ispitanika kontrolne grupe, uparenih po polu i uzrastu, koji nisu imali istoriju glioma i drugih malignih bolesti u ličnoj i porodičnoj anamnezi. Nakon potpisivanja informisanog pristanka, svi bolesnici su popunili epidemiološki upitnik. Za obradu statističkih podataka korišćena je multivarijantna logistička regresija. **Rezultati.** Maligne bolesti su bile češće u studijskoj, nego u kontrolnoj grupi [odds ratio (OR) = 1,821, 95% confidence interval (CI) = 1,004–3,305; p = 0,049]. Najčešći maligni tumori u studijskoj grupi su bili karcinom materice (7%) i karcinom debelog creva (6%), dok su u kontrolnoj grupi najčešći karcinomi bili karcinom pluća (6%) i karcinom materice (7%). Šećerna bolest u porodičnoj anamnezi je bila češća kod bolesnika kontrolne grupe nego kod bolesnika sa gliomom (OR = 0,520, 95% CI = 0,271–0,995; p = 0,048). Takođe, naši rezultati su pokazali da su kardiovaskularne bolesti u porodičnoj anamnezi bile češće u kontrolnoj grupi nego u studijskoj grupi (OR = 0,557, 95% CI = 0,325–0,953; p = 0,033). **Zaključak.** U ovoj studiji slučaj-kontrola, pronašli smo statistički značajnu vezu između porodične istorije malignih bolesti i glioma. Takođe, pronašli smo statistički značajnu inverznu vezu između porodične istorije kardiovaskularnih bolesti i šećerne bolesti i glioma.

Ključne reči:
glioma, porodična istorija bolesti; istorija bolesti, uzimanje; epidemiologija; neoplazme.

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Introduction

Malignant gliomas are the most frequently diagnosed brain tumors in adults [1]. They represent a heterogeneous group of tumors which have histological similarity to glia, such as astrocytes and oligodendrocytes [2]. Gliomas occur in all age groups with predominance of adults over 45 years [3]. The etiology of glioma occurrence is yet unknown [4]. Well-established risk factors for glioma development include older age, male gender, Caucasian race/ethnicity and rare genetic syndromes [5–7].

Genetic predisposition and ionizing radiation affect only a small proportion of the total population, which provide little opportunity for prevention [5]. Some hereditary tumor syndromes are associated with glioma such as Li-Fraumeni, neurofibromatosis (types 1 and 2), tuberous sclerosis, nevoid basal cell carcinoma syndrome, familiar polyposis and von HippelLindau, but the nature of these associations is still unclear [6].

The influence of diseases on family history in the glioma's etiology is uncertain. Genetic factors are poorly understood. A number of studies conducted so far reported that positive family history of malignant diseases increased risk of glioma occurrence [8–15].

Based on all above mentioned, we aimed to investigate the relation among glioma and family history of diseases.

Methods

Study design

The study group consisted of 100 patients (59 males and 41 females), mean age 59.19 ± 10.03 years, with histopathologically verified diagnosis of glioma according to the World Health Organization (WHO) criteria [International Classification of Diseases (ICD)-O-3]. Out of the 100 patients, 78 (78%) had glioblastoma multiforme, 9 (9%) astrocytoma anaplasticum, 5 (5%) oligodendroglioma gradus II, 3 (3%) oligoastrocytima gradus III, 2 (2%) oligoastro-cytoma gradus II and 1 (1%) patients had oligodendroglioma gradus III, 1 (1%) oligodendroglioma anaplasticum gradus III and 1 (1%) ksantoastrocytoma gradus II. The study was realized according to the Declaration of Helsinki and approved by the Ethics Committee of Clinical Centre Kragujevac.

The criteria for inclusion into the study were: patients with confirmed diagnosis of primary, previously untreated glioma. Exclusion criteria 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 from April 1, 2015 to May 30, 2016. The control group included 200 patients matched by gender and age (109 males, mean age 59.32 ± 10.71 years, and 91 females, mean age 58.09 ± 9.12 years) to glioma cases. Controls were individuals admitted to the same institutions for nonmalignant conditions within the same period of time as the cases. Also, control individuals were without glioma and other malignant diseases in personal and family history. All participants signed informed consent.

Data collection

Data was collected by means of questionnaire consisting of sixth parts.The first part of the questionnaire included demographic characteristic of the patients. The second part of the questionnaire included family history of certain diseases (cardiovascular disease, diabetes mellitus, other chronic diseases and family history of malignant diseases including brain tumors). The third part of the questionnaire referred to the personal history of diseases including reproductive risk factors. The fourth part dealt with information on the risks of exposure to environmental risk factors, the fifth included data on habits (smoking, drinking coffee, tea and alcohol consumption) and the sixth part referred to information about nutrition.

Statistical analysis

The initial portion of the statistical analysis included descriptive statistics. For the comparison of qualitative variables between the patients with glioma and the control individuals, chi-square (χ^2) test was used. Categorical variables were presented as frequencies and percentages. Multivariate logistic regression analysis with odds ratio (OR) and 95% confidence intervals (CI) were performed in order to determine the effects of family history of diseases (including malignant diseases, cardiovascular diseases and diabetes mellitus) on the dependent variable (glioma). P value of less than 0.05 was considered statistically significant. Statistical analysis was performed using the SPSS software version 19.0.

Results

Demographic characteristics are provided in Table 1. A total of 100 patients (59 males and 41 females) and 200 control individuals (109 males and 91 females) participated in the study. The mean age of patients was (mean ± standard deviation) 59.19 ± 10.03 years and for controls 58.76 ± 10.01 years ($p = 0.729$). Control individuals were living at the hometown for a shorter time period ($p = 0.035$) and more often changed their place of residence than patients with glioma ($p = 0.007$). Patients with glioma had a higher body weight ($p = 0.002$) and higher body mass index ($p < 0.0005$) than control individuals. In an analysis comparing patients of the study group with control individuals, a significant association ($p < 0.005$) od the disease was observed in relation to the blood group AB.

We observed a statistically significant relation between family history of malignant diseases and glioma (OR = 1.821; 95% CI = 1.004–3.305, $p = 0.049$). In the study group, malignant tumors in familiy history were observed in 31 (31%) patients with glioma and in 38 (19%) patients of the control group.

Table 1

Demographic characteristics of patients with glioma (the study group) and patients in the control group

Variable	Study group (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
All patients	59.19 ± 10.03	58.76 ± 10.01	0.729
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
Blood groups, n (%)			< 0.0005
AB	31 (31)	21 (10.5)	
A	24 (24)	63 (31.5)	0.224
B	10 (10)	28 (14.0)	0.442
O	31 (31)	60 (30)	0.921
Rh factor (-), n (%)	8 (8)	25 (12.5)	0.921

BMI – body mass index; SD – standard deviation.

Table 2

Family history as a risk factor for glioma according to multivariate conditional logistic regression analysis

Variable	Study group (n = 100) n (%)	Control group (n = 200) n (%)	OR (95% CI)	p
Brain tumors	10 (10)	0 (0)	0.000 (0.00-)	0.999
Epilepsia	5 (5)	4 (2)	0.385(0.09–1.67)	0.203
Migraine	6 (6)	13 (6.5)	0.999 (0.32-3.08)	0.998
Neurological diseases	24 (24)	14 (7)	0.641 (0.29–1.42)	0.267
Malignant tumors	38 (38)	31 (15.5)	1.821 (1.00–3.30)	0.049
Diabetes	17 (17)	59 (29.5)	0.520 (0.27–0.99)	0.048
Cardiovascular diseases	31 (31)	102 (51)	0.557 (0.32–0.95)	0.033
Autoimmune diseases	0 (0)	1 (0.5)	5175 (0.000-)	0.999
Chronic diseases	7 (7)	22 (11)	1.687 (0.671-4.238)	0.266
Genetic syndromes	0 (0)	1 (0.5)	2999 (0.000 -)	1.000

OR – odds ratio; CI – confidence interval.

However, statistically significant inverse relation was observed between family history of cardiovascular diseases (OR = 0.557; 95% CI = 0.325–0.953, p = 0.033) and diabetes (OR = 0.520; 95% CI = 0.271–0.995, p = 0.048) and glioma (Table 2). A positive family history of cardiovascular diseases was observed in 31 (31%) patients with glioma, while in the control group 102 (51%) patients had a cardiovascular diseases in the family. Diabetes mellitus in family history was registered in 17 (17%) glioma patients, while in the control group 59 (29.5%) patients had positive family history of diabetes.

Patient with glioma and controls did not differ with respect to epilepsy, migraine, other neurological diseases (stroke, dementia, Parkinson's disease, amyotrophic lateral sclerosis – ALS, vertigo, multiple sclerosis), autoimmune diseases, chronic diseases and genetic syndromes (Table 2). The most common malignant tumors in the study group were cancer of the uterus (7%) and colon cancer (6%), while in the control group the most common cancer were lung cancer (6%) and cancer of the uterus (7%) (Table 3).

Table 3

Family history of cancer by site in the study group (patients with glioma) and the control group

Localization	Study group (n = 100) n (%)	Control group (n = 200) n (%)
Uterus	7 (7)	6 (3)
Kidney	2 (2)	2 (1)
Leukaemia	1 (1)	0 (0)
Breast	5 (5)	4 (2)
Prostate	4 (4)	4 (2)
Colon	6 (6)	5 (2.5)
Mouth	1 (1)	0 (0)
Larynx	2 (2)	1 (3.2)
Lung	0 (0)	12 (6)

Discussion

Our case-control study of 100 cases of histopathologically confirmed glioma demonstrate an association between glioma and family history of malignant diseases, diabetes

and cardiovascular diseases. Malignant diseases in family history were more common in the study group than among patients in the control group (OR = 1.821, 95% CI = 1.004–3.305; p = 0.049). Several studies with similar methodology reported that positive family history of tumors of the central nervous system may be associated with increased risk of glioma. Results of the study conducted by Hill et al. [8] suggested that patients with positive family history of stomach cancer, prostate cancer and Hodgkin's disease had increased risk for glioma development (2-fold), while patients with family history of colon cancer had 1.4-fold risk. Positive family history of colon or prostate cancer increased risk of glioma in individuals aged 18–49 years, while positive family history of stomach cancer or Hodgkin's disease increased risk of glioma in older individuals ($\geq$ 50 years). Risk of astrocytoma is elevated among individuals with positive family history of breast cancer. Also, Hill et al. [8] reported that individuals with two or more relatives with malignant disease had increased risk for glioma development compared with individuals without cancer in family history. Results of Utah Population Database suggested that individuals who had first degree relatives with tumors of central nervous system had elevated risk for glioma, especially women. Moreover, men with positive history of prostate cancer had elevated risk of glioma suggested by results of several study [9–11]. Also, results of these studies suggest that glioma risk was elevated in individuals with positive family history of Hodgkin's disease.

Wrensch et al. [12] observed that positive family history of breast cancer may increase the risk of glioma. Lunch et al. [13] have reported that individuals with brain tumor had 2 or more relatives with breast cancer in 34 families. In one study, lung and breast cancer occurred more often in family members of cases than controls [14]. Results of one study suggest that patients with melanoma had increased risk for glioma [15]. Association of glioma and melanoma may be explained by deletion of common tumor suppressor genes (p16 and p14) [16].

Results of a study of Paunu et al. [17] suggested that families with 2 or more glioma cases had increased risk of glioma (4-fold). Malmer et al. [18] observed that individuals with positive family history of the low grade and the high grade gliomas in first degree relatives had elevated risk for development of these tumors. These results confirmed Scheurer et al [15]. However, results of one study with 416 glioma cases did not show relation between risk of glioma and family history of malignant disease [19].

A family history of malignant disease can be attributed to rare genetic mutation such as polymorphisms of XPD genes and exposure to environmental factors [20, 21].

In our study, we observed a statistically significant inverse relation between family history of diabetes and risk of glioma. Diabetes mellitus in family history was more common among control individuals than among glioma patients (OR = 0.520, 95% = CI 0.271–0.995; p = 0.048). To our best knowledge, this is the first study investigating the relationship between family history of diabetes and risk for glioma occurrence. Other studies investigated relationship of personal history of diabetes with risk of glioma development. A lower risk of glioma associated with diabetes was first reported in a 1965 study reporting a lower frequency of glioma among diabetics versus non-diabetics [22]. The previous studies observed a statistically significant reduced risk of glioma in patients with diabetes type 2 [23–27]. The results of one study reported that increased HbA1c level is associated with decreased glioma risk. The results of an experimental study suggested that the use of metformin in patients with glioma may reduce the risk for its development [28].

The underlying biological pathways that could explain decreased risk of glioma in patients with diabetes are yet unknown. Specific biomarkers of immune function and insulin resistance could provide additional insight on biological mechanisms that may underlie the inverse association between diabetes and glioma risk [27].

Our results showed that cardiovascular diseases in family history were more common in the control group than among patients of the study group (OR = 0.557, 95% CI = 0.325–0.953; p = 0.033). The most common cardiovascular disease in our study was hypertension. Results of one case-control study observed that patients with glioma had higher prevalence of hypertension [29]. Also, a number of researchers concluded that use of some antihypertensive drugs might be potential explanation for such relationship [30].

We did not find statistically significant association between epilepsy, migraine, other neurological diseases, autoimmune and chronic diseases in family history and glioma in the study group. So far, no study examined relation between these diseases and risk of glioma.

This was the first study in our country to examine the relation between family history of diseases and risk of glioma. However, there are some limitations which should be mentioned. Namely, one of limitations of this study is a small number of patients with pathologically confirmed glioma in the study group. Another limitation of the study referes to recall bias, bearing in mind that the answers were collected by means of questionnaire.

Conclusion

In this case-control study, we observed a statistically significant relation between family history of malignant diseases and glioma. Also, we found statistically significant inverse relation between family history of cardiovascular diseases and diabetes and glioma. There is a need for further research on a much larger sample, in order to confirm these findings.

Disclosure

The authors report no conflict of interes.

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