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Potential Risk Factors of Glioblastoma Multiforme in Greek Adults: A Case- Control Study

Nikolaos Andreas Chrysanthakopoulos^{1,2*}, Panagiotis Andreas Chrysanthakopoulos³

¹Dental Surgeon, Oncologist, Specialized in Clinical Oncology, Cytology and Histopathology, Department of Pathological Anatomy, Medical School, University of Athens, Athens, Greece.

²Resident in Maxillofacial and Oral Surgery, 401 General Military Hospital of Athens, Athens, Greece.

³Colonel-Neurosurgeon MD, Director of Neurosurgery Department of 417 Military Hospital of Athens, Athens, Greece.

*Corresponding Author: Nikolaos Andreas Chrysanthakopoulos, Dental Surgeon, Oncologist, Specialized in Clinical Oncology, Cytology and Histopathology, Department of Pathological Anatomy, Medical School, University of Athens, Athens, Greece; Tel: +0030-2610-225288; Email: nikolaos_c@hotmail.com

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Abstract

Aim: The aim of the current report was to assess the association between potential risk factors in the pathogenesis of Glioblastoma Multiforme (GBM) in a Greek adult sample.

Materials and Methods: The study sample consisted of 68 individuals who suffered from GBM and 280 healthy no GBM individuals. Initial diagnosis of GBM based on Magnetic Resonance Imaging (MRI) findings diagnosis, however definitive confirmed by the histopathological examination of the intraoperatively removed tumor or its parts, using traditional histological, cytologic and histochemical methods. The associations between known potential risk factors of GBM and the GBM risk was assessed using univariate and multivariate logistic regression analysis models.

Results: The application of logistic regression model showed that higher Socio-Economic Status (SES) ($p=0.032$, $OR=3.79$, 95% $CI=1.36-8.61$), previous infection with Cytomegalovirus (CMV) ($p=0.048$, $OR=3.11$, 95% $CI=1.12-6.89$), and previous Traumatic Brain Injury (TBI) ($p=0.028$, $OR=5.58$, 95% $CI=2.14-11.40$), were statistically significantly associated with GBM risk.

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Conclusion: Higher SES, previous CMV infection and previous TBI were significantly associated with the risk of developing GBM.

Keywords

Gliomas; Glioblastoma Multiforme; Risk Factors; Adults

Introduction

Glioblastoma, also known as Glioblastoma Multiforme (GBM) or diffuse astrocytoma, WHO grade IV, is the most common adult primary malignant brain tumor [1]. It accounts for more than 60% of all brain tumor in adults, for 50% of all gliomas in all age groups and its frequency varies between 12%-15% of all intracranial tumors and 50 to 60% of astrocytic tumors [2,3]. It is characterized by severe clinical signs and symptoms, extremely poor prognosis, despite the variety of modern therapies, and shows a great morphological and genetical heterogeneity. GBM patients' prognosis shows that 10% survive within three years, only 3 to 5% survive for more than 5 years, whereas the median survival after the final diagnosis has been observed to be 12 to 15 months [1,4]. The main reasons for the poor prognosis is that GBM is an extremely invasive and proliferative tumor with highly abnormal vascularization, displays resistant to the common chemotherapy and radiotherapy and in general is difficult to be completely removed surgically [5]. GBM is classified into two types, primary or secondary as a result of a malignant transformation from a lower grade brain tumor and/or with mutation in the gene of Isocitrate Dehydrogenase (IDH), whereas according to the gene expression profile is classified to the following histopathological types Classical, Proneural, Neural and Mesenchymal [6]. 90% of GBM cases develop de-novo, primary glioblastoma, from normal glial cells by multistep tumorigenesis. The remaining 10% are secondary neoplasm, developing through progression from low-grade tumors, diffuse or anaplastic astrocytomas or oligodendrogliomas, which takes about 4-5 years [7]. Secondary GBM is diagnosed mostly in individuals with the mean age 39 years, grows more slowly and has a better prognosis. GBM, which develops de novo, grows within 3 months [8]. Although the genetic basis, as well as the molecular pathways underlying development of primary and secondary GBMs are different, these two types show no morphological differences [9,10].

GBM is rare tumor with global incidence of less than 10/100,000 people, however its poor prognosis makes it a crucial public health issue [11]. In the USA, GBM has an annual incidence of 5.26/100,000 population or 17,000 new diagnoses/year, is more common tumor in the 8th decade of life the primary type mainly, whereas the secondary affects younger ages [3,12]. The number of recorded GBM cases in Europe and America were 3.19/100,000 adults each year and the incidence rate in males in comparison to females were at the level of 1.26:1 [11,13,14].

GBM shows a peak incidence between 55 to 84 years of age [15], whereas in another study was observed a peak incidence between 55 to 60 years [13]. Anaplastic astrocytoma and GBM increase in incidence with age, peaking in the 75 to 84 years age group [16].

The etiology of GBM has not been fully clarified and still remains unclear. Genetic influences in combination with environmental risk factors have been suggested as pathogenic factors of GBM [17]. GBM is believed to be a spontaneous tumor, despite the fact that medical history describes development of glioma in related persons [18]. The familial form of GBM is described for 1% of cases [19]. However, the genetic background for development of this type of GBM is different from those arising spontaneously [17]. GBM may also occur in the process of genetic diseases such as tuberous sclerosis [20]. Turcot syndrome, Multiple Endocrine Neoplasia Type IIA (MEN IIA), Li Fraumeni syndrome, and Neurofibromatosis type I (NF1) [21-23]. Acquired head injuries, which occurred as a result of a brain contusion, may predispose to the initiation of GBM [24]. Among women, a higher risk of GBM has been observed in postmenopausal females and a hypothesis on the implication of gender hormones in GBM development was suggested [25]. Incidence of GBM is also related to height and Body Mass Index (BMI), as high values of those two variables increase the risk of GBM incidence [26]. Viruses, such as Human Cytomegalovirus (HCMV), are also believed to be among the etiologic factors for gliomas development as shows tropism for glial cells. Ionizing radiation is one of the physical factors that increase the possibility of developing GBM. Potentially risk factors for GBM development are considered chemicals agents such as polycyclic aromatic compounds, pesticides, and solvents. Electromagnetic fields and certain metals are also considered to be implicated in glioma development. The use of a cell phone does not increase the risk of developing GBM, but the effect of long-term use of cell phones is still undetermined [27]. GBM can be considered as an occupational disease for individuals who are employed in the rubber and petrochemical industry as are considered to be at a higher risk of glioma incidence [28]. The aim of the present case-control study was to assess the role of potential risk factors in GBM development in a sample of Greek adults.

Materials and Methods

Study Sample

208 individuals, GBM patients-cases and healthy-controls, 136 males and 72 females, aged 50 to 79 years were recruited from 2 private practices and a hospital neurosurgery clinic and constituted the study sample. Cases and controls were responded to a medical questionnaire. The study was conducted from September 2016 to December 2019.

Participant's Selection Criteria

68 individuals who suffered from GBM referred by the mentioned clinic and the private practices accepted the invitation to participate in the study. The primary diagnosis of GBM was based on Magnetic Resonance Imaging (MRI) but definitive diagnosis was based on histopathological examination of the intraoperatively removed tumor or its parts, using traditional histological, cytologic and histochemical methods [29]. In case the neurosurgical tumor resection was not possible, Fine Needle Aspiration (FNA) biopsy was performed [30].

In GBM patients that were previously affected by Traumatic Brain Injury (TBI) the following criteria were established which are suggestive of a causal association: the injury must be severe enough to cause a tissue repair procedure to commence, the traumatic injury area should correspond directly with the location of the subsequent GBM, and there should be a gap of at least 1 year between the brain injury and the appearance of the tumor. A longer latent period is considered to be a stronger evidence of a possible causal association between TBI and GBM [31].

HCMV detection of previous infection was based on serum samples that were tested for the presence of HCMV IgM and IgG antibodies using Enzyme-Linked Immunosorbent Assay method (ELISA), according to medical records of the cases and controls, as Real-time Polymerase Chain Reaction (Rt-PCR) technique was not available decades ago [32]. 280 healthy individuals who were referred by the mentioned practices determined the control group. Both groups, cases and controls, were selected from the same city population in order to avoid or eliminate possible selection biases which can lead to biased secondary associations. To avoid such outcomes a statistical approach for confounding control is the selection of healthy individuals to be based on GBM patients' environment, such as friends, colleagues, etc. To be more specific cases and controls were matched regarding their gender, age, and smoking status (current/previous smokers and never smokers). For each GBM patient, four healthy individuals with the same gender and of the same age (± 4 years) were selected. For eight of the 280 controls, no cases were found to match the mentioned criteria. In the study protocol were not included individuals with brain metastases due to a different primary location.

Questionnaire

All participants were responded to a self-administered questionnaire that included variables such as age, gender, smoking status (active/never-smokers), socio-economic status (income/monthly $\geq$ or $<$ 1,000 €), educational level (graduated from University/College or Primary/Elementary school) and data regarding their general medical history with reference to medication, several chronic systemic and hereditary disorders. Cases and controls medical records were used in cases where participants could not remember details from their medical history related to the variables examined.

Clinically, most patients (n=58) present de novo grade IV lesions (primary GBMs), whereas only a small rate of cases (14.7%) show progression from less aggressive diffuse astrocytoma's (WHO grade II) and anaplastic astrocytoma's (WHO grade III) (secondary GBMs).

Ethical Consideration

The current retrospective case-control study should not be reviewed and approved by authorized Greek committees (Greek Dental Associations, Ministry of Health, etc.) as it was not an experimental one, and was carried out according to the World Medical Association Declaration of Helsinki. Cases and controls who accepted the invitation to participate in the study protocol and signed an informed consent form were selected.

Statistical Analysis

Females, never smokers, low socio-economic status, low educational level, absence of medical history of the following conditions: GBM family history, neurofibromatosis, Li Fraumeni syndrome, previous infections with HCMV, TBI and controls were classified as 0, whereas age groups distribution was classified as 0,1,2 and for ages 50-59, 60-69 and 70-79, respectively. For assessing the association between the independent indices examined and the GBM risk, separately was performed the univariate analysis. Logistic regression analysis model was carried out to assess the associations between the dependent variable, GBM, and independent ones. Unadjusted and adjusted Odds Ratios (OR's) and 95% Confidence Interval (CI) were also assessed.

Statistical analysis was carried out by SPSS statistical package (SPSS PC19.0, SPSS, Inc., Chicago, IL, USA), and a p-value less than 5% ($p < 0.05$) was considered to be statistically significant.

Results

68 individuals, 48 males and 20 females suffered from GBM and 280 individuals 176 males and 104 females consisted the control group. Cases and controls ranged in age from 50 to 79 years old and the mean age was 68 ± 3 years. Smoking, previous infection with HCMV, and previous TBI were found to be significantly associated with GBM risk according to univariate analysis (Table 1). Table 1 also presents unadjusted OR's and 95% CI. The regression model, 1a step showed that higher SES ($p=0.052$) and previous TBI ($p=0.028$) were significantly associated with GBM risk (Table 2). Table 2 also shows adjusted OR's and 95% CI. The final model (step 9a), showed that higher SES ($p=0.032$, OR=3.79, 95% CI= 1.36-8.61), previous infection with HCMV ($p=0.048$, OR= 3.11 95% CI=1.12-6.89) and previous TBI ($p=0.028$, OR= 5.58, 95% CI=2.14-11.40), were significantly associated with the risk for GBM development (Table 2).

Variables	Cases	Controls	p-value	Odds Ratio	95% Confidence
	(no) (%)	(no) (%)	value	(OR)	Interval (CI)
Gender: Males	48 (70.6)	176 (62.9)			
Females	20 (29.4)	104 (37.1)	0.232	1.42	0.80-2.52
Age (years):					
50-59	11 (16.2)	36 (12.8)			
60-69	35 (51.5)	150 (53.6)	0.055	-	-
70-79	22 (32.4)	94 (33.6)			
Socio-economic Status: Low	30 (44.1)	158 (56.4)			
High	38 (55.9)	122 (43.6)	0.068	0.61	0.36-1.04
Educational Level: Low	40 (58.8)	156 (55.7)			
High	28 (41.2)	124 (44.3)	0.643	1.14	0.66-1.94
Smoking: No	24 (35.3)	138 (49.3)			
Yes	44 (64.7)	142 (50.7)	0.038*	0.56	0.32-0.97
GBM Family History					
No	62 (91.2)	244 (87.1)			
Yes	6 (8.8)	36 (12.9)	0.36	1.53	0.62-3.78
Neurofibromatosis					
No	63 (92.6)	265 (94.6)			
Yes	5 (7.4)	15 (5.4)	0.526	0.71	0.25-2.04
Li Fraumeni Syndrome					
No	60 (88.2)	242 (86.4)			
Yes	8 (11.8)	38 (13.6)	0.693	1.18	0.52-2.66
Prev. inf. HCMV: No	28 (41.2)	157 (56.1)			
Yes	40 (58.8)	123 (43.9)	0.027*	0.55	0.32-0.94
Prev. tr. br. inj. No	39 (57.4)	222 (79.3)			
Yes	29 (42.6)	58 (20.7)	0.000*	0.35	0.20-0.95

Table 1: Univariate analysis of cases and controls regarding each independent variable examined.

Variables in the Equation									
		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
								Lower	Upper
Step 1 ^a	Gender	463	602	592	1	442	629	193	2,048
	Age	856	468	3,346	1	67	2,353	941	5,885
	Socioecon.st	1,177	626	3,539	1	52	3,246	952	8,069
	Smok.stat	1,086	566	2,023	1	179	1,090	359	3,307
	Fam.history	1,700	1,083	2,463	1	117	3,475	655	6,773
	Neurofibrom	1,549	869	3,173	1	75	2,705	856	5,259
	Li fraumeni s	549	745	542	1	462	1,731	402	4,461
	Infect.cmv	722	701	1,062	1	83	2,059	521	5,130
	tr.brain.inj	2,352	695	6,444	1	35	4,902	1,896	11,016
	Constant	5,241	1,283	16,684	1	0	5		
a. Variable(s) entered on step 1: gender, age, socioecon.st, smok.stat., fam.history, neurofibrom, li fraumeni s, infect.cmv, tr..brain.inj									
Variables in the Equation									
		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
								Lower	Upper
Step 9 ^a	socioecon.st	1,756	738	2,662	1	32*	3,792	1,363	8,612
	infect.cmv	1,237	773	6,623	1	48*	3,109	1,123	6,884
	tr.brain.inj.	2,719	750	7,071	1	28*	5,580	2,144	11,399
	Constant	2,659	603	19,459	1	00	070		
a. Variable(s) entered on step 9: gender, age, socioecon.st, smok.stat., fam.history, neurofibrom, li fraumeni s, infect.cmv, tr.brain,inj.									
* p-value : statistically significant									

Table 2: Presentation of association between potentially risk factors and GBM according to Enter (first step-1a) and Wald (last step 9a) method of multivariate logistic regression analysis model.

Discussion

The current research indicated that higher SES, previous HCMV infection and previous TBI were significantly statistically associated with risk for GBM development. SES is a known confounder, however is associated with risk of various cancer types because of correlation between SES and causal factors or increased case confirmation, or both. Previous reports recorded a positive association between SES and GBM risk [33-39]. That strong association is

not likely to represent a confirmed effect because GBM is a rapidly progressive and lethal disease and that some of the proposed GBM risk factors could be correlated with SES, such as gender, age, smoking status, educational level [37]. Similarly, Khanolkar et al., reported that the potential explanations for those findings could be the completeness of cancer recording and detection bias [38]. Further research is needed to clarify the mechanism of this association.

Cancer can be considered an age-related disease because the incidence of most cancers increases with age [40]. It has been shown that an increased risk of GBM is associated with advanced age [13,15,37,39,41]. Moreover, anaplastic astrocytoma and GBM increase in incidence with age, with a peak in the 75-84 age group, whereas Nelson et al., found that age was not independently associated with development of GBM [15,39,42]. The current research recorded no association between those indices examined. The mentioned contradictory results could be attributed to the fact that age is also regarded as a confounding variable.

It has been shown that GBM incidence varies according to gender. Males show increased risk of GBM compared to females, finding that was not in line with the outcomes of the current report [15,37,39,41,43,44]. In general, gliomas are more common in males than females, with the exception of pilocytic astrocytoma, which occurs at similar proportions in males and females [16,28,45,46].

Little evidence exists to support a possible association between any lifestyle factors, such as smoking and an increased risk for gliomas. Although smoking has proven to be in relation to certain types of tumors in lung, rectum, etc., reports up to day were not able to identify any relevant association between smoking and brain tumors and the main cause is that gliomas are not a conventional disease in the general population. This denotes that cohort studies cannot collect sufficient information, which in turn defines that data can only be gathered from case-control studies [26]. Additional causes are the inadequate number of cases in different studies, the incomplete research hypothesis and imperfect criteria for patient selection [47]. According to the outcomes of the current research no association was observed between smoking and GBM risk, finding that was in line with those from previous reports but were not in agreement with the outcomes of other similar studies [42,47,50,54-57].

It has been indicated that brain tumour risk differs by educational background as higher education has been associated with increased risk of low grade glioma, but not for high-grade glioma or meningioma, although results are conflicting [36,38]. For glioma, the Incidence Rate Ratios (IRR) increased with increasing level of education in both genders, and more consistently in males than females [38]. No association was found in the present study regarding those variables examined.

It is possible that genetic influences in combination with environmental risk factors are implicated in GBM pathogenesis [17]. The initial suggestion that a single gene was the only causative factor has been rejected as various characteristic genetic alterations have been recorded in sporadic astrocytoma's, especially GBM [58,59]. Several syndromes have been

associated with risk for GBM development. The most important and the associated genes are type 1 and 2 Neurofibromatosis (NF1,2), Li Fraumeni syndrome (TP53 mutations), Turcot syndrome (APC and hMLH1/hPSM2 mutations), Tuberous Sclerosis (TSC 1,2) and Retinoblastoma (RB1), [13,20,21,23,28,53,54,60].

NF1 is an autosomal dominant disease which is characterized by multiple neurofibromas, cafeau lait spots on the skin and an increased incidence of diffuse astrocytomas, GBMs and optic nerve gliomas, whereas NF2 is characterized by dysplastic and neoplastic lesions of the Schwann and meningeal cells and glia [13]. Li Fraumeni syndrome is a rare, autosomal dominant, hereditary disorder, is characterized by early onset of cancer, a wide variety of types of cancers and development of multiple cancers such as breast cancer, sarcomas, osteosarcomas and brain tumors, especially GBMs [28]. The present study recorded no association between any type of those syndromes and risk for GBM development. The familial cases of GBM support a genetic basis for GBM and as already mentioned, gliomas and specifically GBM, occur in association with several hereditary tumor syndromes. Given the rare incidence of GBM in the general population and the even rarer appearance within the same family, a genetic basis needs to be further investigated. A family member with a glioma could represent a risk factor for the other family members. The familial existence of GBM in the absence of those neurological tumor syndromes can be present, despite the fact that is a rare incident, as has been assessed to be 1% of GBM cases and could be attributed to the fact that GBM is a relatively rare tumor so the incidence of two sporadic cases occurring in the same family may be low [17,19,22,61,62]. Moreover, the genetic predisposition has been found in only 5 to 10 % of brain tumor cases and the susceptibility gene is still unidentified [47]. Moreover, the genetic background for development of this type of GBM is different from those arising spontaneously [17].

Wrensch et al., observed that OR of a Primary Brain Tumor (PBT) in family members of patients with PBT was 2.3, finding that was confirmed by Malmer et al. [63,64]. The last author investigated if genetic factors are implicated in a higher incidence of brain tumors in families having one member already affected by the disease and found that Standardized Incidence Ratio (SIR) among spouses of High Grade Gliomas (HGG) patients was the same as in the general population, whereas SIR was 2.3 for 1st degree relatives of patients diagnosed with HGG [65].

Segregation analysis showed that family congregation could explain only 5% of glioma cases and that a recessive gene model matches in about 2% of all cases [66]. On the other hand, family congregation was not confirmed by a similar study in Iceland [67].

Recent Genome Wide Association Studies (GWAS), have indicated Single Nucleotide Polymorphisms (SNPs) that grant increased predisposition to developing glioma. A remarkable such SNP is located on chromosome 8q24.21 within the locus of a long non coding RNA (lncRNA) named CCDC26, which increases glioma risk approximately 5 times [68-70]. No association between family history of GBM and risk for GBM development was found in the

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current report. Eventually, the role of predisposing genetic factors in gliomagenesis is still not well determined and further research is needed. Previous researches have recorded that TBI and glial scarring were implicated as predisposing factors in malignant glial tumors patients [71-75]. However, some of those were case reports and it is possible that in cases of a positive association, the relation is either non-significant or inconsistent [13]. A strong association was recorded in the current study, finding that was in agreement with those from previous reports, in which a clear evidence for such a causative role was presented [73,75-77]. Other authors suggested that GBM following a traumatic cerebral contusion is possible [24,78]. In some of those cases, the histopathological diagnosis was a prolongation of the gliotic scar of the tumor and persisting splinters were found in the glioma nests many years after TBI [72,75]. Post-traumatic gliomas have been reported, but in none of those previous reports has been documented absence of a tumor at the time of the brain injury. Only in one study was reported a case of a post-traumatic glioma with radiographic evidence of only a contusion prior to the development of the tumor [73]. On the other hand, some researchers have not observed any significant association between brain trauma and gliomas risk [79-81].

Although epidemiologic studies may not be convincing, a histopathological basis for development of post-traumatic gliomas has been proposed. At the site of TBI an inflammatory response is observed which is characterized by recruitment of resident brain microglia, myeloid inflammatory cells, peripheral neutrophils, monocytes, and eosinophils to the injury location within hours and can remain for extended periods of time [82-84]. Those inflammatory cells can contribute to oncogenesis due to the generation of Reactive Oxygen Species (ROS), which have mutagenic effects, or due to release of growth factors, cytokines and chemokines [83]. Neural stem cells have an oncogenic potential, whereas neurons and astrocytes, are able to result in GBM development by incurring de-differentiation guided by genetic alterations [85-87]. A supposed model has been suggested that links neuro-inflammation to mutagenesis in neural stem and progenitor cells migrating to the injury location, leading to their neoplastic transformation and glioma initiation [88]. GBM may also establish after neurosurgical operations due to the concentration of Myelin Basic Protein (MBP) in the brain [89].

Human Cytomegalovirus (HCMV or HHV-5), is also considered to be among the risk or etiologic factors for glioma development. HCMV shows tropism for glial cells and causes congenital encephalitis and multi-organ changes in immunosuppressed adults. The virus encodes proteins, such as IE1, US28 and GB, which are implicated in the activation of cellular signalling pathways involved in mitogenesis, inflammation, apoptosis, angiogenesis and mutagenesis. HCMV gene products cause dysregulation of signalling pathways involved in tumorigenesis, such as PDGFR, Akt, STAT3, but also causes aberrations in glial cell and monocyte functions [90,91]. Although an association between HCMV and GBM risk was first reported in 2002 and supported by a large number of observational and experimental studies [90,91-101] there is still a high degree of inconsistency in the literature regarding the detection of viral traits in Central Neural System tumors [42,102-107]. The possible association was based on histopathological findings such as infection of GBM cells with HCMV, activation of

cellular signalling pathways and the onco-modulatory effects of HCMV [94-99,108]. While the mentioned experiments show that those HCMV genes have the potential to be oncogenic, the question as to whether HCMV is associated with GBM risk remains unclear. The current report recorded a significantly association between previous HCMV infection and risk for GBM development.

Limitations of this study include the small number of participants who developed GBM, the small sample size of at risk individuals, its retro-prospective design and the possible selection, random biases and the effect of known and unknown confounders which could lead to biased secondary associations regarding the variables examined. In addition, since this study was initially designed to identify or confirm risk factors for this cancer, risk factors that could be important may not have been ascertained. Strengths of this study was the histologic confirmation of all GBM cases, and population-based investigation of a relatively homogeneous sample. Ascertainment of all GBM cases was enhanced because of the comprehensive surveillance, review of detailed hospital records and tumor registry reports.

Conclusion

In conclusion, the results showed that higher SES, previous CMV infection and previous TBI were significantly associated with the risk of developing GBM.

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