Increased risk of neoplasia among relatives of glioma patients

A. González-Aguilar [a,d], P. Gutiérrez-Castrellón [e], E. Briceño [b], D. Rembao-Bojórquez [c], M.E. Alonso-Vilatela [a], A. Rasmussen [a]

INCREASED RISK OF NEOPLASIA AMONG RELATIVES OF GLIOMA PATIENTS

Summary. Introduction. *Some previous studies have suggested familial aggregation of gliomas, although the results have not always been replicated.* Subjects and methods. *In the present study of a Mexican population, we compared 100 cases of glioma with 124 healthy unrelated controls, as well as their 1st, 2nd and 3rd degree relatives (*n *= 3,575 and 4,520 respectively).* Results. *The relatives of the cases had a significantly higher risk of developing brain tumors than the relatives of controls (OR = 5.3;* p *< 0.05; 95% CI = 1.1-25.7), and their risk of developing any cancer was also increased (OR = 2;* p *< 0.05; 95% CI = 1.16-3.51), this risk was twofold for men when compared to females (OR = 2;* p *< 0.05; 95% CI = 1.15-3.37).* Conclusion. *The present study supports familial aggregation of brain tumors and warrants further research into their genetic etiology. [REV NEUROL 2008; 47: 343-6]*

Key words. *Familial aggregation. Glioma. Hereditary cancer syndromes.*

INTRODUCTION

The term 'glioma' has been used to describe a subset of primary brain tumors with morphology and gene expression similar to normal glial tissue. Most glioma arise as sporadic tumors, however, they can also be a manifestation of a more complex hereditary cancer syndrome. Families with hereditary cancer syndromes transmit the increased risk of tumors in a Mendelian fashion, attributable to mutations in a single predisposing gene [1-5]. Epidemiologic studies of brain tumors have implicated both genetic and environmental factors in the etiology of the disease [6-10], however, most of the putative risk factors have not been confirmed, with the possible exception of ionizing radiation as an environmental factor [11]. Multiple studies in diverse populations have tried to analyze the genetic contribution to gliomagenesis. One such approach is the analysis of familial aggregation, which represents a higher-than-expected frequency of brain tumors in the relatives of cases as compared to the relatives of controls [12-14]. There are anecdotal reports of brain tumors in relatives of patients with glioma, albeit this is considered an infrequent event [15,16]. Harvald-Hauge [17] and Aita [18] concluded that genetic factors were not relevant in the genesis of brain neoplasia, except in the case of neurophacomatosis. On the other hand, several studies support a hereditary transmission of gliomas [19-23], and several authors have suggested that relatives of glioma patients also have an increased risk of other types of cancer [24-28], and they predispose for a high grade glioma, survival and prognostic inside the same families [29,30]. The retrospective analysis of those reports, ruled out that the increased risk was secondary to autosomal dominant hereditary cancer syndromes [25,31-36].

A recent Swedish study [37], which analyzed glioma-glioma association, divided the cases according to the histologic grade of the tumor, and they found that the risk (SIR) for 1st degree relatives of low grade glioma cases was 3.65-7.0, with a maximum of 9 for sibs under the age of 40. The same study was unable to find an increased risk for relatives of high grade glioma cases.

SUBJECTS AND METHODS

We designed a descriptive, transversal, case-control study of a Mexican population. All the patients with a confirmed histopathologic diagnosis of glioma that attended the neurooncology clinic of the Instituto Nacional de Neurología y Neurocirugía between February 1 and December 31, 2004 were invited to participate. We excluded all the cases that fulfilled clinical criteria of a familial cancer syndrome or neurophacomatosis. Controls were recruited among the healthy relatives of patients attending the genetics clinic of the same institution according to the inclusion criteria of a protocol designed to create a DNA bank of healthy Mexican Mestizos. A total of 100 glioma cases with 3575 relatives and 124 unaffected controls with 4250 relatives were ascertained. Informed consent was obtained according to the requirements of the Institute's IRB. Each case and control was interviewed by one of the researchers (AG) according to a structured questionnaire that included sociodemographic information and a pedigree that included information of first, second and third degree relatives. Vital status, history of tumors and cause of death was recorded for each individual. For all cases, the histopathologic confirmation of tumor type and WHO stage was obtained. In the case of the relatives, we divided tumors into two groups: intracranial and extracranial neoplasia. It was not possible to obtain histological information about the intracranial tumors, therefore, we ignore the exact number of gliomas in the relatives. Something similar happened for extracranial tumors, in most cases only anatomic location was recorded.

The risk of developing a tumor was estimated by odds ratio (OR) with a 95% confidence interval (95% CI). We analyzed the risk related to gender, family history of cancer, family history of intracranial tumor, number of family members affected by cancer or intracranial tumors and by WHO stage. Statistical significance was evaluated with χ^2 test, Fisher's exact test and Mann-Whitney *U* test, with a level of significance of $p < 0.05$. All the data were analyzed with the SPSS v. 10.0 software.

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[a] Department of Neurogenetics and Molecular Biology. [b] Neurology Division. [c] Neuropathology Department. Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez. [d] Facultad de Estudios Superiores Zaragoza. UNAM. [e] Research Direction. Instituto Nacional de Pediatría. Mexico City, México.

Corresponding author: Dra. Astrid Rasmussen. Department of Biochemistry and Molecular Biology. University of Oklahoma Health Sciences Center. 975 NE 10th Street, BRC 458. Oklahoma City, OK 73104, USA. Fax: (+1) 405 271 3910. E-mail: astrid-rasmussen@ouhsc.edu

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Table I. Risk of intracranial tumor or cancer in relatives of glioma cases vs. controls

	Cases	OR	CI 95%	*p*	Controls	OR	95% CI
Male/Female	58/42	2.0 [a]	1.15-3.37 [a]	< 0.05 [a]	51/73	0.73	0.57-0.9
Positive family history of cancer	46	2.0 [a]	1.16-3.51 [a]	< 0.05 [a]	37	0.7	0.54-0.9
Negative family history of cancer	54	0.4	0.28-0.85	> 0.05	88	0.76	0.61-0.95
Positive family history of intracranial neoplasia	8	5.3 [a]	1.10-25.77 [a]	< 0.05 [a]	2	0.3	0.1-1.2
Negative family history of intracranial neoplasia	92	0.1	0.03-0.90	> 0.05	121	0.9	0.87-0.99

95% CI: 95% confidence interval; OR: odds ratio. [a] Statistically significant values.

RESULTS

Of the 100 cases, 46 had a family history of cancer, of which 8 tumors were intracranial; of the 124 controls, 37 had cancer history in their family and only 2 of them had a family member with an intracranial neoplasia. The risk of a relative of a case of developing any type of cancer was increased when compared to the relatives of controls (OR = 2.0; $p < 0.05$; CI 95% = 1.16-3.51), and the risk of intracranial tumor was even higher (OR = 5.3; $p < 0.05$; CI 95% = 1.10-25.77). When gender was taken into account, we found that male gender increased the risk of tumors (OR = 2.0; $p < 0.05$; CI 95% = 1.15-3.37) (Table I). There was also a significant difference in the number of affected individuals per family, the cases had a higher number of affected relatives ($p < 0.05$) (Tables II and III). The analysis of the pedigrees did not show evidence of Mendelian inheritance, and the affected relatives were 1st, 2nd and 3rd degree relatives, supporting a multifactorial transmission.

Table II. Number of family members affected with any other neoplasia and divided according to histologic grade of the proband's glioma.

	Cases	Controls	*p*	Low grade glioma	High grade glioma	*p*
Without affected relatives	54 (54%)	86 (69.4%)	> 0.05	23	30	> 0.05
One affected relative	26(26%)	26 (21%)	> 0.05	12	14	> 0.05
2 or more affected relatives	20 (20%) [a]	12 (9.6%) [a]	< 0.05 [a]	12	9	> 0.05

[a] Significant values.

Table III. Risk of intracranial or extracranial neoplasia depending on histologic tumor grade.

Tumor type	Low grade	OR	95% CI	High grade	OR	95% CI
Male/Female	24/23	0.75	0.26-1.3	34/19	1.2	0.87-1.92
Positive family history of cancer	23	1.12	0.74-1.70	23	0.9	0.61-1.30
Negative family history of cancer	24	0.8	0.58-1.34	30	1.11	0.76-1.61
Positive family history of intracranial neoplasia	4	1.0	0.51-2.21	4	0.9	0.45-1.92
Negative family history of intracranial neoplasia	43	0.9	0.45-1.93	49	1.06	0.51-2.1

95% CI: 95% confidence interval; OR: odds ratio.

DISCUSSION

To the extent of our knowledge, this is the first study analyzing familial aggregation of glioma in Mexico. Our results support the notion that the relatives of a glioma patient have a much higher risk of developing intracranial tumors than controls, with an odds ratio of 5.3. In general, previous reports support the existence of familial aggregation of brain tumors, even if there are some contradictory results [30]. Our results are in concordance with most authors, although the risk we identified is one of the highest reported. These findings strengthen the hypothesis of a genetic background of glioma.

We also found a significant association (OR = 2.0) between glioma and a positive family history of any type of cancer. These results are similar to previous reports that have analyzed the family history of patients with brain tumors, which have found that the reported frequency of cancer is higher amongst relatives of glioma cases when compared to controls [25,31]. One possible interpretation of these results is that family members share a common genetic risk, which is modified by environmental factors such as ionizing radiation, infection or exposure to toxins. It is the combination of these factors that determines the number of affected family members and the types of cancer that affect them. We tried to identify a transmission pattern of glioma and/or cancer risk, comparing the number and type of affected relatives of cases versus controls. We found a statistically significant ($p < 0.05$) difference in the number of affected family members, such that cases have more affected relatives than cases.

We also found that males had a higher risk of glioma when compared to females (OR = 2.0), and that this difference persisted when we divided gliomas in high grade and low grade tumors. This gender-difference has not been reported in previous studies. One possible explanation is that in the group of patients we studied, only a low proportion of females have out-of-home jobs, suggesting that males may have a higher laboral exposure to environmental risk factors. This hypothesis should be tested in a larger study controlled for laboral status and ideally for non-genetic risk factor exposure, keeping in mind that gliomas have a male preponderance. Yet another possible explanation is the participation of hormonal (v.gr. estrogenic) factors as a protective influence in the development of these tumors.

We analyzed whether a correlation could be found between the number of affected family members and histologic grade of the tumors, and found no significant differences. Only one previous study has taken this approach, and contrary to our results,

they report that the risk for 1st degree relatives of low grade glioma was increased, with a maximum risk for younger sibs under the age of 40. These results prompted the authors to propose that low grade and high grade gliomas are two different nosologic entities, with low grade gliomas being associated with a more important genetic risk possibly transmitted in an autosomal recessive ways [35-37]. Our results are discordant with this report, we cannot rule out the possibility that this is related to a different study design: our study analyzed the association of glioma and any intracranial neoplasia, while the previous report confirmed glioma-glioma associations. On the other hand, our study is a transversal analysis of a of a small population of cases and controls attending one reference center, while the Swedish study is a prospective study of a population cohort with 39 years of follow-up.

Segregation analysis was inconsistent with simple Mendelian inheritance, both for glioma-intracranial tumor families and for glioma-any cancer families. We excluded all the cases with phacomatosis as well as families that fulfilled criteria for any of the hereditary cancer syndromes, in order to avoid a bias towards autosomal dominant transmission of the tumors. The affected individuals were related in 1st, 2nd or 3rd degree to the proband, suggesting a multifactorial transmission of the risk. The epigenetic and environmental factors determining affectedness were not assessed in the present study.

The main limitation of our study is that we were unable to verify the histologic type of the reported intracranial tumors affecting the proband's relatives. A future study will aim at obtaining this information, in order to verify our findings.

Our study supports an important genetic contribution to the development of glioma, and it's association with an increased risk of intracranial and other neoplasia in the relatives of glioma patients. These findings warrant further research into the familial aggregation of glioma in other populations.

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INCREMENTO EN EL RIESGO DE NEOPLASIA ENTRE FAMILIARES DE PACIENTES CON GLIOMA

Resumen. Introducción. *Estudios previos han sugerido que existe agregación familiar de gliomas; sin embargo, los resultados no siempre han sido replicables.* Sujetos y métodos. *En el presente estudio de una población mexicana, comparamos 100 casos de glioma con 124 controles sanos no emparentados, así como sus familiares de primer, segundo y tercer grado (*n = *3.575 y 4.520, respectivamente).* Resultados. *Los familiares de los casos tuvieron un riesgo significativamente mayor de desarrollar tumores cerebrales que los familiares de los controles (*odds ratio, *OR = 5,3;* p < *0,05; intervalo de confianza al 95%, IC 95% = 1,1-25,7), su riesgo de desarrollar cualquier tipo de cáncer también fue mayor (OR = 2;* p < *0,05; IC 95% = 1,16-3,51), y este riesgo fue el doble para varones que para mujeres (OR = 2;* p < *0,05; IC 95% = 1,15-3,37).* Conclusión. *El presente estudio apoya la existencia de agregación familiar de neoplasias cerebrales y obliga a profundizar en el estudio de su etiología genética. [REV NEUROL 2008; 47: 343-6]*

Palabras clave. *Agregación familiar. Glioma. Síndromes de cáncer hereditario.*