History of Atopy Confers Improved Outcomes In IDH Mutant And Wildtype Low-Grade Glioma

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Research Article

Keywords: atopy, allergy, IDH, low grade glioma, BDNF

Posted Date: August 18th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-784423/v1>

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Abstract

Purpose:

A history of atopy or allergy has been shown to be protective against the development of glioma, however the effect of atopy on patient outcomes, especially in conjunction with the survival benefit associated with IDH mutation, has not yet been investigated, and is the focus of the study we present here.

Methods:

Low grade glioma (LGG) data from the TCGA was downloaded, along with IDH, TERT, 1p/19q and ATRX mutational status and genetic alterations. History of asthma, eczema, hay fever, animal, or food allergies, as documented in TCGA, was used to determine patient atopy status. Patients with missing variables were excluded from the study.

Results:

374 LGG studies were included. Patients with a history of atopy demonstrated longer overall survival (OS) compared to those without (145.3 vs. 81.5 months, $p=0.0195$). IDH mutant patients with atopy had longer OS compared those without atopy (158.8 vs. 85 months, $p=0.035$). Multivariate cox regression analysis demonstrated that the effects of atopy on survival were independent of IDH and histological grade, ($p=0.002$, HR 0.257, 95% 0.109-0.604), ($p<0.001$, HR 0.217, 95% 0.107-0.444), and ($p=0.004$, HR 2.72, 95% 1.373-5.397), respectively. In terms of treatment outcomes, patients with atopy did not differ in treatment response compared to their counterpart. Pathway analysis demonstrated an upstream activation of the BDNF pathway ($p=0.00027$).

Conclusion:

A history of atopy confers a survival benefit in patients with diffuse low-grade glioma. Activation of the BDNF pathway may drive the observed differences.

Introduction

Gliomas are the most common primary central nervous system (CNS) malignancies in adults accounting for almost 77% of primary brain tumors [1]. They are typically diagnosed based on histopathology and clinical criteria and classified by WHO (World Health Organization) criteria grade I-IV, with Diffuse Low-grade glioma classified as WHO grade II & III, dependent on key molecular alterations [2, 3]. Diffuse low-grade glioma patients have a better overall survival outcome (~ 6–7 years) compared to high-grade glioma (WHO grade IV), glioblastoma (GBM), patients (12–16 months) [4–7]. Greater than 70% of diffuse LGGs harbor a mutation in isocitrate dehydrogenase (IDH), which has been associated a survival advantage to the patients [2, 8–11]. Although IDH mutant (IDHm) LGG patients have a better prognosis, the immune microenvironment of patients harboring the IDH mutation is vastly different compared to the IDH wildtype (IDHwt) form of the disease [9]. IDHm LGGs have reduced innate and adaptive immune

response seen in the form of decreased NK cell activity, decreased tumor-infiltrating lymphocytes, and increased circulating myeloid-derived tumor suppressor cells [8–10]. Much research has been dedicated to reversing this phenomenon with immunotherapy to increase patient outcomes [12].

Given the importance of immune driven defense against cancer, there has been considerable interest in understanding the effects of a “hyperactive” immune system, such as that which is seen in patients with a history of allergy or atopy, and the likelihood of these patients to develop various cancers, including glioma [13–16]. Although the association between atopic conditions such as allergy, asthma, and eczema has been investigated across various malignancies, the findings have remained relatively inconsistent throughout. Atopic conditions have been shown to have protective effects such as a lower incidence rate, or improved clinical outcomes in certain malignancies such as low-grade glioma, colorectal cancer, childhood leukemia, and pancreatic cancer [15]. Yet in other cancers such as lung cancer and melanoma, the findings remain inconclusive, or simply demonstrate the opposite effect [15, 16]. While a history of atopy & allergy has been associated with protective features in LGG, clinical outcomes related studies remain insufficient or incomplete. To our knowledge only one such study exists [17] however, given the vast heterogeneity of LGG, both phenotypic and genetic, the effect of atopy is not yet understood in the context of the IDH1 or IDH2 mutation, which in itself is known to be associated with improved clinical outcomes such as survival, when compared to wildtype glioma [9, 10]. In this study, we use data from The Cancer Genome Atlas (TCGA) to analyze outcomes in low-grade glioma patients in the context of IDH mutations and tumor grade status to determine whether a history of atopy has any true influence on patient outcomes.

Methods

Patients and Data Collection

Using the TCGAbiolinks R package, Low-Grade Glioma (LGG) data were downloaded from the Genomics Data Commons Data Portal along with clinical data pertaining to each patient. Mutational data for IDH1, IDH2, TERT, ATRX, 1p19q co-deletion, was downloaded from cBioPortal for Cancer Genomics for each patient. Clinical variables included patient demographics such as age, gender, race, days to death, days to last follow up, and a history of atopy defined as having a history of one of the following: Asthma, eczema, food allergy, animal allergy, hay fever, or mold/dust energy. Inclusion criteria included adult LGG patients for which TCGA reported data on IDH mutational status, and atopy variables were available. Patients with incomplete or unavailable key data points were excluded from the analysis (Fig. 1). Days to the last follow-up, and days to death for each patient were also collected, along with treatment outcomes for patients undergoing treatment. Outcomes were stratified by TCGA as “Complete Remission/Response”, “Partial Remission/Response”, “Progressive Disease”, and “Stable Disease”.

Survival, Multivariate, and Statistical Analysis

Kaplan Meier survival curves were generated using Graphpad Prism for Macintosh, and the Log-Rank test was applied to determine statistical significance at a threshold of $P < 0.05$. Univariate and multivariate

Cox Regression analyses were performed using R packages *Survminer* and *Survival* with statistical significance again defined as $P < 0.05$.

Differential Gene Expression and Pathway Analysis

Raw RNAseq expression count data was downloaded for the LGG study sample from the TCGA using the *TCGAbiolinks* package. Data normalization and differential gene expression analysis were performed using the *DESeq2* package. Parameters for significance in expression changes were set to a fold change of ± 1.5 , with a false discovery rate (q-value) of less than 0.05. Genes that met the significance criteria were then included in the pathway analysis performed using *Ingenuity Pathway Analysis (IPA)* from *QIAGEN Inc.* Statistical significance for pathway analysis was set at $P < 0.05$.

Results

514 diffuse LGG patients were accessed from the PanCancer Atlas study within the TCGA. After careful review, 374 studies with both clinical and mutational data, were included for further analysis. In our study cohort, patients harboring either a mutation in IDH1 or IDH2 (83.2%, $n = 311$), were shown to have a significantly higher overall survival with median survival in the IDHm sample of 101.3 months, compared to 22.8 in the IDHwt group ($p < 0.0001$, HR 0.22, 95% 0.12–0.42) (Fig. 2A). When looking at all 374 patients, a history of allergy or atopy (23.3%, $n = 87$) was also associated with a significantly longer overall survival, with a median survival of 145.3 months in atopic patients, compared to 81.5 months in patients without a history of atopy ($p = 0.0195$, HR 0.40, 95% 0.22–0.74) (Fig. 2B). In the context of IDHm patients only, patients with atopy demonstrated an additional survival benefit with a median survival of 158.8 months compared to 85 months ($p = 0.0335$, HR 0.34, 95% 0.16–0.72) (Fig. 2C). A history of atopy was also associated with an increased median overall survival in the IDHwt patient cohort, 145.3 months vs. 21.7 months (with atopy vs. no atopy IDHwt; $p = 0.2150$, HR 0.49, 95% 0.18–1.39) (Fig. 2D).

Histological grade was also taken into consideration as a potential confounding factor and therefore was analyzed with survival curves. Approximately an even number of samples were either identified as WHO Grade II, or WHO Grade III ($n = 185$; 49.5%, and $n = 189$; 50.5%, respectively). In concordance with the literature, a significantly higher median overall survival was demonstrated in patients with WHO Grade II vs. Grade III glioma, 127.5 months compared to 56.6 ($p < 0.0001$, HR 0.30, 95% 0.20–0.46) (Fig. 3A). Furthermore, a history of atopy was again associated with longer median survival in each subdivision (Grade II, and Grade III). In patients with WHO Grade II glioma and a history of atopy, median survival was 158.8 months compared to 103.8, ($p = 0.0024$, HR 0.97, 95% 0.31–3.0) (Fig. 3B) while in WHO Grade III patients with atopy the median survival was 145.3 months compared to 47.8 ($p = 0.0013$, HR 0.19, 95% 0.10–0.34) (Fig. 3C). Females with and without atopy were observed to have better overall survival, however, this was not statistically significant, and unlikely to drive the differences in survival attributable to atopy (Fig. 4A & B).

Additionally, both univariate and multivariate Cox regression analyses were conducted to elucidate the effect of atopy on survival independent of mutations that are known to either positively or negatively

influence overall survival outcomes. Univariate analysis of the IDH, TERT, 1p19q co-deletion, and ATRX mutation status demonstrated survival benefits associated with IDH mutation and the 1p19q co-deletion. Only 2 patients in the study tested positive for TERT mutations, rendering it insignificant. In our study population, ATRX appeared to have no significant effect on survival. Univariate testing showed a statistically significant effect of a history of atopy on survival, while a higher WHO grade was associated with lower overall survival. Assessing these variables with a multivariate analysis demonstrated that a history of atopy conferred a survival benefit independent of IDH mutation, and also independent of the histological grade of the tumor. ATRX mutations and 1p19q co-deletion status were not observed to independently influence survival in the context of IDH, atopy, and histological grade. This data is summarized in Table 2.

Data regarding treatment and treatment related outcomes were available for 50.8% ($n = 190$) patients in our study cohort. Outcomes were defined as patients having complete remission/response, partial remission/response, progressive disease, or stable disease. For those patients with available outcomes data, 21% of patients ($n = 40$) had a history of atopy. In the atopy cohort, 40% ($n = 16$) of patients experienced complete remission/response, 22.5% ($n = 9$) experienced partial remission/response, 10% ($n = 4$) experienced progressive disease, and 27.5% ($n = 11$) experienced stable disease. These outcomes were not significantly different compared to the without atopy group, of which 30.7% ($n = 46$) patients demonstrated complete remission/response, 26% ($n = 39$) experienced a partial response, 15.3% ($n = 23$) demonstrated progressive disease, and 28% ($n = 42$) of patients demonstrated stable disease (Table 3).

Further, differential gene expression analysis of RNAseq data was performed on all IDHm patients with and without atopy, given the larger sample size. Results of the differential gene expression were introduced to the Ingenuity Pathway Analysis platform (IPA), where the top canonical pathways were identified (Fig. 5A). IPA results also illustrated a relative upstream activation of the brain-derived neurotrophic factor (BDNF) pathway in those patients with a positive history of atopy ($p = 0.00027$) (Fig. 5B).

Discussion

The association between cancer and conditions of atopy and allergy such as eczema, allergy (environmental, or food), hay fever, and asthma have long been studied to determine whether there appears to be a consistent trend between those who harbor these conditions and the development of cancers. While the results have been inconsistent across some malignancies, the literature offers relatively strong support in the case of glioma, with multiple observational and meta-analysis studies demonstrating an inverse relationship between patients with atopic conditions and the development of glioma [18–28]. As many of these studies have been observational epidemiological studies in nature, the mechanism for decreased risk of glioma in patients with atopy has not yet been described or elucidated. Studies conducted by Wiemels et al. have looked at IgE levels in patients with a history of atopy/allergy, initially demonstrating lower IgE levels in glioma patients, however, follow up studies remained inconclusive as treatment with temozolomide was thought to influence IgE levels [23, 24].

Despite numerous studies demonstrating the negative correlation between atopy and glioma development, outcomes-related data remains insufficient [28–32]. Furthermore, while this correlation has garnered strong support in the literature, there are some studies that do not strongly support this finding [33]. However, to our knowledge, only one study looking at outcomes of glioma patients with atopy was done by Lehrer et al [17]. In this study, the authors demonstrate a survival advantage in patients with atopy, independent of TERT mutations, 1p19q co-deletion, and histological grade. While the study demonstrated a strong association between patients with a history of atopy and increased overall survival, we were curious as to whether the survival benefits seen in atopic patients may be explained by the increased survival benefit conferred by the IDH mutation, as IDH status was not a covariate in the published study. In our study, we first demonstrated a survival benefit in patients harboring IDH1/2 mutations as evidenced and supported by the literature. Second, we demonstrated that patients harboring an IDH1/2 mutation, and carrying a clinical history of atopy/allergy, had an even longer overall survival than IDHm patients with no atopy (Fig. 1C). Third, we identified that a history of atopy is associated with increased survival via some mechanism independent of other mutations and genetic variations such as IDH mutation, histological grade (WHO Grade II vs. III), 1p19q co-deletion, and ATRX mutational status.

To investigate key pathways that may play a role in driving these survival benefits in diffuse LGG patients with a history of glioma, we performed a differential gene expression and pathway analysis. We focused on only the IDHm population in our sample as the majority, 79% ($n = 296$), of patients in our study cohort, had either the IDH1 or IDH2 mutation. Using IPA, our analysis of canonical pathways was largely non-specific, highlighting activation of cAMP-mediated signaling, GNRH signaling, CREB signaling in neurons, amongst others. Interestingly however, our upstream regulator pathway analysis showed activation in the brain-derived neurotrophic factor (BDNF) pathway. Increased expression of BDNF by eosinophils is found to be crucial for atopic diseases such as allergic asthma and dermatitis [34]. Interestingly, BDNF's expression is documented to have both oncogenic and tumor-suppressive properties depending on the form of BDNF and on the cancer type [35, 36]. Multiple studies have elucidated the potential role of eosinophilia and BDNF pathway activation in gliomas, for example, clinical studies conducted in postoperative IL-2 treated patients found enhanced GBM patient survival to be associated with tissue eosinophilia [12, 37, 38]. Furthermore, studies conducted in melanoma and in glioma indicated that activation of hypothalamic BDNF augments T-cell cytotoxicity to confer an anti-cancer phenotype [36, 39]. However, to fully understand the importance of BDNF pathway and eosinophilia in both LGG and GBM patient survival warrants further investigations.

In our study using TCGA data, we encountered a few limitations and attempt to address these. One limitation encountered was the fact that there is no data on the extent of resection for LGG surgeries. This data would ideally be used as a covariate in our multivariate analysis as the extent of surgical resection has been demonstrated to be a predictor of clinical outcomes [40–43]. Another limitation encountered is the unavailable WHO Grade I data. While diffuse low-grade gliomas are classified often by the IDH mutation and 1p19q status, our results show that atopy confers a survival benefit independent of these molecular alterations. Including Grade I gliomas would have been an interesting addition to our sample size, and would have strengthened our results should they have remained unchanged. Lastly, TCGA does

not have atopy/allergy data for the glioblastoma (WHO Grade IV) studies. This would have also been a valuable addition to our study as the previous metaanalyses examining the effects of atopy, allergy and glioma have focused on gliomas as a whole. Analyzing GBM specifically would have also helped to identify whether the BDNF pathway is similarly upregulated in GBM patients with atopy as we see in diffuse LGG patients with atopy.

Conclusion

Altogether our study demonstrates a survival benefit in patients harboring IDH1/2 mutations which is further improved by a history of atopy. Moreover, we suggest that a history of atopy confers an increased survival potentially via a mechanism such as the activation of the BDNF pathway. This pathway may be an independent determinant of improved outcomes in this patient cohort, in addition to other mutations and genetic variations in glioma such as IDH mutation, histological grade (WHO Grade II vs. III), 1p19q co-deletion, and ATRX mutational status.

Declarations

Funding: Not applicable

Conflict of Interest: All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Availability of Data & Material: All data used is publicly available from the TCGA and cBioPortal.

Code Availability: Not applicable

Authors' contributions: EJ & XZ conceived and designed the study. EJ collected the data and performed the analyses. EJ, XZ, PS, JA, RS wrote the manuscript. AH & POZ provided critical revision and performed edits. POZ provided final approval.

Ethics Approval: Not applicable

Consent to Participate: Not applicable

Consent for Publication: All authors listed contributing to the manuscript give consent for publication.

ACKNOWLEDGMENTS:

EJ is funded by the Dean's Research Fellowship. *Awarded by the Dean of School of Medicine at the University of Pittsburgh School of Medicine to aspiring Physician-Scientists.*

XZ is funded by the Physician-Scientist Incubator Program. *The University of Pittsburgh holds a Physician Scientist Institutional Award from the Burroughs Welcome Fund.*

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Tables

Table 1: Patient Demographics and Comparisons

Parameters	n	%	P value
All Patients			
Males	217	58.00%	-
Females	157	42.00%	-
Mean Age (Years)	42.2		-
Dead at Last Follow Up	52	13.90%	-
Average Follow Up (Months)	20.3		-
Patients With Atopy	87	23.30%	-
Males	44	50.10%	0.108
Females	43	49.40%	-
Mean Age (Years)	41.1		0.194
Pre-Op KPS >80	52	86.70%	0.324
Race/Ethnicity			-
Non-Hispanic White	81	93.10%	0.003
Black/African American	3	3.45%	-
Hispanic/Latino	1	1.15%	-
Asian	0	-	-
American Indian	0	-	-
Unknown	2	2.30%	-
Atopy Criteria Met			
Asthma	16	18.40%	-
Allergy	6	6.90%	-
Eczema	6	6.90%	-
Hay Fever	20	23.00%	-
Dust Allergy	2	2.30%	-
Food Allergy	14	16.10%	-
Animal Allergy	5	5.74%	-
One or More	18	20.70%	-

Patients Without Atopy	287	76.70%	-
Males	173	60.30%	-
Females	114	39.70%	-
Mean Age (Years)	42.5		-
Pre-Op KPS	154	91.10%	-
Race/Ethnicity			
Non-Hispanic White	228	79.40%	-
Black/African American	11	3.83%	-
Hispanic/Latino	25	8.71%	-
Asian	4	1.39%	-
American Indian	1	0.35%	-
Unknown	18	6.27%	-

Table 2: Multivariate Analysis of Prognostic Parameters

Parameters	Univariate			Multivariate	
	N=374	HR (95%CI)	P value	HR (95%CI)	P value
IDH Status					
Mutation	311 (83.2%)	0.163 (0.088-0.302)	<0.001	0.217 (0.107-0.444)	<0.001
TERT Status					
Mutation	2 (0.5%)	Undefined	1	-	-
1p19q Status					
Co-Deletion	126 (33.7%)	0.467 (0.227-0.958)	0.038	0.585 (0.271-1.262)	0.172
ATRX Status					
Mutation	142 (38.0%)	0.873 (0.502-1.516)	0.629	-	-
Atopy Status					
Positive History	87 (23.3%)	0.398 (0.179-0.886)	0.024	0.257 (0.109-0.604)	0.002
Histological Grade					
Grade II	185 (49.5%)	3.571 (1.889-6.751)	<0.001	2.722 (1.373-5.397)	0.004
Grade III	189 (50.5%)				

Table 3: Comparison of Treatment Response

Parameters	With Atopy (n=40)	Without Atopy (n=150)	P Value
	n (%)		
Complete Remission/Response	16 (40.0%)	46 (30.7%)	0.263
Partial Remission/Response	9 (22.5%)	39 (26.0%)	0.651
Progressive Disease	4 (10.0%)	23 (15.3%)	0.391
Stable Disease	11 (27.5%)	42 (28.0%)	0.95

Figures

Figure 1

Flow Diagram of TCGA studies included in the final analysis.

Figure 2

Kaplan Meier survival curves depicting overall survival of patients. A) Comparison of IDH Mutant LGG patients to IDH Wildtype demonstrated a statistically significant increased overall survival in the IDH mutant population. B) Comparison of patients with a history of atopy to those without demonstrated a significantly longer overall survival amongst patients with a history of atopy. C) Comparison of IDH mutant patients with atopy to IDH mutant patients without atopy showed statistically significant increase in overall survival in IDH mutant patients with atopy. D) Comparison of IDH wildtype patients with atopy to those without atopy demonstrating an increase in overall survival in IDH mutant patients that have a history of atopy, which was non-significant.

Figure 3

Kaplan Meier survival curves comparing histological grade in addition to atopy. A) Patients with WHO Grade II glioma experienced a statistically longer overall survival compared to those with WHO Grade III. B & C, a history of atopy confers a statistically significant increase in overall survival in both WHO Grade II and Grade III patients.

Figure 4

Kaplan Meier survival curves comparing gender and atopy. A) No statistically significant difference in survival outcomes between males and females without atopy. B) In patients with atopy, there is also no significant difference in outcomes between males and females.

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Figure 5

Ingenuity Pathway Analysis results demonstrating A) top 5 most significantly altered canonical pathways and B) graphical summary of the most significant canonical pathways and upstream regulators, depicting the involvement and activation of the BDNF pathway.