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Original Article

Analysis of geographical distribution of high-grade glioma diagnoses in the Alessandria province: pilot study preliminary results

Analisi della distribuzione geografica delle diagnosi di glioma ad alto grado nella provincia di Alessandria: risultati preliminari di uno studio pilota

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Key words: gliomas, glioblastoma multiforme, geographical distribution, environmental factors.

ABSTRACT

Background: one under-researched line of investigation is gliomas, which are a group of malignant brain tumours with highly poor prognoses. Despite efforts to identify environmental risk factors for gliomas, their etiology still remains unclear. It turns out that several future developments are needed in order to understand other potential risk factors. To this end, the primary objective of the present pilot study is to conduct an assessment of the spatial distribution of high-grade brain tumor cases in the province of Alessandria, where possible risk factors such as the presence of chemical industries and asbestiform fibers are found.
Materials and Methods: the study sample consisted of all patients diagnosed with high-grade glioma between January 2018 and April 2023, residents in the province of Alessandria at the time of diagnosis and referred to the health facilities of the "Azienda Sanitaria Locale di Alessandria" and the "Azienda Universitario-Ospedaliera di Alessandria". Biographical and pathological history variables were collected, and finally, data were processed in aggregate and anonymized form. A total of 103 deceased patients were enrolled, stratified by age and type of diagnosis.
Results: it was seen that the city with the most cases was Alessandria, with 27 diagnoses found during the period under review (26.2%), followed by cities of Acqui Terme, Casale Monferrato, and Novi Ligure with seven diagnoses (6.8%). Preliminary results presented in this paper were compared with data already published.
Conclusions: analyses performed to arrive at an initial geographical distribution of high-grade glioma diagnoses are consistent relative to the population density of each municipality considered.

Background: una linea di ricerca poco studiata è quella dei gliomi, che sono un gruppo di tumori cerebrali maligni con prognosi molto sfavorevoli. Nonostante gli sforzi per identificare i fattori di rischio ambientali per i gliomi, la loro eziologia rimane ancora poco chiara. Risultano sono necessari diversi sviluppi futuri per comprendere altri potenziali fattori di rischio. A tal fine, l'obiettivo primario del presente studio pilota è quello di effettuare una valutazione della distribuzione geografica dei casi di tumore cerebrale di alto grado nella provincia di Alessandria, dove si riscontrano possibili fattori di rischio come la presenza di industrie chimiche e fibre asbestiformi.
Materiali e Metodi: il campione di studio è costituito da tutti i pazienti con diagnosi di glioma di alto grado tra gennaio 2018 e aprile 2023, residenti in provincia di Alessandria al momento della diagnosi e afferenti alle strutture sanitarie dell'Azienda Sanitaria Locale di Alessandria e dell'Azienda Ospedaliera di Alessandria. Sono state raccolte variabili anagrafiche e patologiche e infine i dati sono stati elaborati in forma aggregata e anonimizzata. Sono stati arruolati 103 pazienti deceduti, stratificati per età e tipo di diagnosi.
Risultati: è emerso che la città con il maggior numero di casi è Alessandria, con 27 diagnosi riscontrate nel periodo in esame (26,2%), seguita dalle città di Acqui Terme, Casale Monferrato e Novi Ligure con sette diagnosi (6,8%). I risultati preliminari presentati in questo lavoro sono stati confrontati con i dati già pubblicati.
Conclusioni: le analisi effettuate per arrivare a una prima distribuzione geografica delle diagnosi di glioma di alto grado sono coerenti rispetto alla densità di popolazione di ciascun comune considerato.

Introduction

Gliomas are a group of malignant brain tumours believed to originate from neuronal stem-derived glial progenitor cells. As a whole, this group of diseases has an annual incidence of 4-11 cases per 100,000 population, with a higher frequency in industrialized and high-income countries,[1] and a median age of onset around 50-60 years of age.[2] Brain tumours typically have highly poor prognoses, even in individuals younger than 40 years of age, in whom they are very rare, however.[3] Gliomas are considered the most common primary tumour of the Central Nervous System (CNS) in adults and account for 70-80% of all malignant brain tumours. They are usually classified into grade I, II, III and IV according to malignancy.[4] Some examples of grade III and IV gliomas are: grade III astrocytoma, oligodendroglioma, ependymoma, and meningioma, which have survival of two to five years; glioblastoma and diffuse hemispheric glioma[5] grade IV, which have the poorest prognosis, with a median survival of one to two years in cases where maximal safe surgical resection and Temozolomide (TMZ) chemotherapy are possible.[1]

Since the 2016 WHO classification, traditional histological criteria have been supplemented with genomic biomarkers. Recently, the new WHO classification is based solely on molecular profiling.[2] Some of the most frequently identified mutations are as follows: mutation of the gene for Isocitrate Dehydrogenase (IDH) 1 and 2, which is associated with a survival benefit in patients with high-grade glioma;[2] co-deletion of the chromosomal arms 1p and 19q (1p/19q), which is a diagnostic marker for oligodendrogliomas and a strong predictor of response to chemotherapy and radiotherapy; methylation of the O6-Methylguanine DNA Methyltransferase (MGMT) promoter gene, which is an independent predictor of survival and response to TMZ combination radiotherapy.[2] The combination of the presence of IDH mutation and MGMT methylation may further increase survival outcomes.[6] However, it is hypothesized that sequential accumulation of genetic aberrations, de-regulation of growth factor signalling pathways, and other genetic abnormalities contribute to a continuum from low-grade (II) to high-grade (IV) glioma.[7] Despite efforts to identify environmental risk factors for glioma, its etiology remains unclear.[3]

Zumel-Marne and colleagues published a systematic review linking possible exposure to environmental factors and brain tumour diagnosis, particularly with regard to heavy metals, consumption of water from the water supply system, second-hand smoke, environmental pollution, pesticide exposure, parents' occupation, food diet (related to red meat consumption)[8] and, lastly, to radiofrequency electromagnetic waves. In particular, pesticides are certainly carcinogenic to the central nervous system; this finding has been consistent among existing studies and confirmed by a review and meta-analysis. A recent study showed an increased risk of brain tumours with exposure to carbamate pesticides.[9] Evidence regarding the potential carcinogenicity of Radiofrequency Radiations (RFRs) from cell phones is increasing. In 2011, the International Agency for Research on Cancer (IARC) classified RFRs from cell phones as possible human carcinogens and also highlighted an increased incidence of glioblastoma in recent years compared to other gliomas, but there is still no scientific evidence in the literature linking this increase with RFRs.[10] High doses of ionizing radiation are an established environmental risk factor associated with glioma development,[11] while for other occupational, environmental, and lifestyle exposures there is still little scientific evidence available. Chlorinated industrial solvents, for example, have long been suspected to be a cause of glioma because of their ability to cross the blood-brain barrier due to their high solubility in fat, however, the results of the INTEROCC project demonstrated no association between glioma occurrence and exposure to a specific group of solvents.[12]

In order to perform our work, we focused on the geographical area of the Alessandria province, as our goal is to investigate possible exposures to environmental factors of several types (including radiation, chemical pollutants, pesticides, and other factors).

Materials and Methods

This pilot study aims to conduct an assessment of the spatial distribution of high-grade brain tumour cases in the Alessandria province, where possible environmental risk factors are found.

Study design and ethical approval

This pilot study is a retrospective, multicentre, non-industrial observational study in accordance with M.D. 30/11/2021 (no-profit trial). It was sponsored by the Research and Innovation Department (DAIRI), Azienda Ospedaliero-Universitaria SS. Antonio e Biagio e Cesare Arrigo di Alessandria (AOU AL), and Azienda Sanitaria Locale di Alessandria (ASL AL), and involved a total of three clinical centres in Alessandria's province. This pilot study has been submitted to the SS. Antonio and Biagio and Cesare Arrigo Ethics Committee (Protocol n. Asl21.Neuro.23.01).

Population and variables collected

The study sample consists of all patients diagnosed with incident high-grade glioma between January 2018 and April 2023, taken at the Pathologic Anatomy of the AOU AL, who were residents in the province of Alessandria at the time of diagnosis and were afferent to the health facilities of the ASL AL and the AOU AL. Patients older than 18 years old, with a histological diagnosis of high-grade glioma (grade III astrocytoma, grade III oligodendroglioma, grade III ependymoma, grade III meningioma, grade IV glioblastoma, and grade IV diffuse hemispheric glioma) carried out between January 2018 and April 2023 at the Pathologic Anatomy of the AOU AL, and residents in the province of Alessandria at the time of diagnosis were included.

Biographical variables (age, gender, municipality, and address of residence at the time of diagnosis), pathological history (type of diagnosis of high-grade glioma, date of diagnosis of high-grade glioma), and molecular analysis (IDH1, IDH2, Ki67, p53, and any other mutations sought) were collected. All addresses of residence with their house numbers were also collected; these variables will be the basis for a future georeferencing analysis once all data have been collected, including those of patients not yet enrolled to date, at the end of the clinical trial.

Statistical analysis

Data were processed in anonymized and aggregated form. Continuous variables with normal distribution were presented as mean and Standard Deviation (SD), while those with non-normal distribution were presented as median and Interquartile Range (IQR). Categorical variables were represented as frequencies and percentages. Associations between categorical variables were tested

using the Chi-square test or Fisher's exact test. Patient survival analyses followed the Kaplan-Meier methodology. All analyses were performed with Statistical Package version 25 IBM SPSS® for Windows® software (Armonk, NY, USA: IBM Corp.)

Results

Preliminary statistical analyses were performed on the first 103 enrolled patients, all of whom were deceased upon enrolment. A summary of preliminary descriptive analyses regarding the general characteristics of patients were collected in Table 1. Men (57.3%) were more frequent than women (42.7%) in the population considered. Moreover, this type of rare tumour resulted to be much more frequent in patients aged >65 years (64.1%) than in patients aged 65 or younger, with a median age of 69 years (IQR=61-75). Grade IV glioblastoma appears to be the most predominant high-grade glioma in the CNS (89.3%). The percentages of the per-year deaths among the total number of enrolled patients are the following: 2018 (5.8%), 2019 (11.6%), 2020 (17.5%), 2021 (31.1%), 2022 (17.5%), and 2023 (16.5%), with an annual mean of 17.2 deaths ±8.64 (Table 1).

In 2023, three new cases were diagnosed, it can be observed that the trend is similar to the first year of observation, slightly decreasing compared to the other years except for 2021, the year in which the drop is more pronounced: in the first four months of 2018 there were four diagnoses, in 2019 there were six diagnoses, seven diagnoses in 2020, 12 in 2021, and six in 2022. It is noted that the three deaths recorded in 2023 correspond to the 3 diagnoses made in the first four months of that year.

Preliminary descriptive analyses concerning the residence of 103 patients enrolled were collected in Table 2. In particular, it was seen that the city with the most cases was Alessandria, with 27 diagnoses found during the period under review (26.2%), followed by the cities of Acqui Terme, Casale Monferrato, and Novi Ligure with 7 diagnoses (6.8%). In the cities of Ovada and Tortona, only five diagnoses were found (4.9%), in Valenza four diagnoses (3.9%), in Castellazzo

Table 1. The 103 patients enrolled in preliminary descriptive analysis.

	Frequency (n)	Percentage (%)
Gender		
Men	59	57.3
Women	44	42.7
Age		
>65 years	66	64.1
≤65 years	37	35.9
Median age	69.00 (61-75)*	
High-grade glioma type		
Glioblastoma (IV)	92	89.3
Astrocytoma (III)	9	8.7
Oligodendroglioma (III)	2	2
Death period		
Year 2018	6	5.8
Year 2019	12	11.6
Year 2020	18	17.5
Year 2021	32	31.1
Year 2022	18	17.5
Year 2023 (Jan-Aug)	16	16.5
Months between diagnosis and death		
>65 years	6 months (3-11.25)*	
≤65 years	10 months (4.50-15.50)*	

*Median (Interquartile Range, IQR).

Table 2. Preliminary analysis on the geographical distribution in towns.

Residence	Frequency (n)	Residents number
Alessandria	27	91,059
Acqui Terme	7	18,967
Casale Monferrato	7	32,204
Novi Ligure	7	27,252
Ovada	5	10,779
Tortona	5	26,432
Valenza	4	18,025
Castellazzo Bormida	4	4,461
Arquata Scrivia	2	6,256
Castelnuovo Scrivia	2	4,862
Molare	2	1,978
Sezzadio	2	1,151
Balzola	1	1,234
Bergamasco	1	694
Bosco Marengo	1	2,204
Brignano-Frascata	1	423
Capriata d'Orba	1	1,764
Carrega Ligure	1	86
Cassano Spinola	1	1,853
Cassine	1	2,801
Castelletto Monferrato	1	1,469
Cellamonte	1	465
Frassinello Monferrato	1	464
Gavi	1	4,415
Grondona	1	472
Melazzo	1	1,219
Mombello Monferrato	1	911
Mongiardino Ligure	1	151
Mornese	1	694
Orsara Bormida	1	388
Pasturana	1	1,289
Pecetto di Valenza	1	1,183
Pontecurone	1	3,457
Ponzone	1	1,007
Quattordio	1	1,461
Rosignano Monferrato	1	1,418
Sala Monferrato	1	332
Sale	1	3,880
San Salvatore Monferrato	1	3,998
Silvano d'Orba	1	1,893
Strevi	1	1,928
Villanova Monferrato	1	1,718

Bormida four diagnoses (3.9%), and in Arquata Scrivia, Castelnuovo Scrivia, Molare, and Sezzadio only two diagnoses (1.9%).

A preliminary survival analysis was carried out, which revealed that the median Overall Survival (OS) is eight months (95% CI 6-9 months). Furthermore, discriminating by place of residence, there was no statistical significance in the OS of Alessandria's residents, compared to other municipalities of the district (n=76, p-value=0.801). On the other hand, performing a survival analysis by stratifying patients by age, it was found that in patients aged £65 years, the median survival was approximately 10 months (Confidence Interval, CI 95%=8-12 months), while in patients aged >65 years, the median survival was approximately 6 months (CI 95% =4-8 months).

In a final analysis, only three patients (2.9%) tested positive for the IDH1 gene mutation, compared to 98 negative (95.2%) and two in which this mutation had not been assessed (1.9%); on the other hand, the IDH2 gene mutation was found in only one case (1.0%), compared to 98 negative (95.1%) and four in which it had not been assessed (3.9%). Methylation of the MGMT gene was found in 46 cases (44.7%), while it was absent in 50 cases (48.5%); in seven it was not assessed (6.8%). Of the 46 positives, the methylation index was <50% in 39 of them (84.8%), while it was ≥50% in seven positives (15.2%). The median OS in patients found to be positive for the IDH1 mutation and for the MGMT methylation (n=3) is 15 months. Co-deletion of chromosome arms 1p and 19q (1p/19q) occurred in 3 cases (2.9%), while it was absent in 13 cases (12.6%) and was not assessed in 87 cases (84.5%). Ki67 proliferative index of a tumour is an indicator of cell viability and, consequently, cell proliferation; it was positive in 91 patients (88.3%), while in a single case, it was negative (1.0%) and in 11 it was not assessed (10.7%). Of the 91 cases in which it was positive, in 67 of them (73.6%) proliferation was <50%, and in 20 of them (22.0%) proliferation was ≥50%, in four cases the value was not available as it was not required in clinical practice analyses (missing value =4.4%). The p53 protein was present in 60 (58.3%) of the 103 high-grade gliomas examined, while it was absent in 13 of them (12.6%) and, finally, in 30 of them it was not assessed (29.1%). This protein, in the 60 cases in which it was found to be positive, had a frequency <50% in 43 cases (71.7%) and a frequency ≥50%, in 7 cases (11.6%), in the remaining 10 cases (16.7%) the value was not available. Finally, the presence or absence of the GFAP and ATRX proteins was assessed dichotomously, with the GFAP protein being present in 53 cases (51.5%) and the ATRX protein in 25 cases (24.3%).

Discussion

Preliminary results presented in this paper were compared with data already available in scientific literature, as they allowed the observation of a first overview of the Alessandria province with regard to a rare tumour, high-grade gliomas. A report published in 2019, by Istituto Superiore di Sanità (ISS), highlighted that for grade IV glioblastoma, the new cases incidence is slightly higher in men than in women.[13] These data are consistent and confirmed by this preliminary analysis, as out of 103 total patients, 57.3% were men. The age range at which grade IV glioblastoma mainly onset is indicated in the literature as 45 to 75 years; the preliminary results obtained confirm this trend, as there were only three diagnoses below 45 years and 25 diagnoses above 75 years. The observed onset appears to have a different range, with more elderly patients, as all high-grade gliomas were taken into account and not just the single neoplasm previously mentioned. With regard to the geographical distribution, looking at the patients' residences, it was seen that, as expected, more diagnoses of high-grade glioma occurred in Alessandria, as it is the largest city in the province with about 92,000 inhabitants. It is immediately followed by the municipalities of Casale Monferrato, which has about 32,300 inhabitants, Novi Ligure, with about 27,200 inhabitants, and Acqui Terme, with about 19,000 inhabitants. In these three municipalities mentioned, seven diagnoses occurred during the period analysed (2018-2023), despite the different number of inhabitants, as shown by the ISTAT data.[14] The analysis proceeded with Ovada (approximately 11,000 inhabitants) and Tortona (approximately 26,400 inhabitants): again, there was parity in the number of diagnoses (n=5) over the period indicated (2018-2023), although they differ in number of inhabitants. Some important data, which could give rise to confirmation only after the geographical distribution had been analysed by georeferencing, are those found in municipalities with a lower population density. In particular, the municipalities of Castellazzo Bormida (n=4 diagnoses), with about 4,460 inhabitants, Molare (n=2 diagnoses), with about 2,000 inhabitants, and Sezzadio (n=2 diagnoses), with about 1,150 inhabitants, were analysed. In these towns, the hypothesis that the incidence is higher is certainly very strong, but it will be confirmed with more reliable data and more robust analyses once the data collection has been completed and all patients who fell within the study's inclusion/exclusion criteria have been enrolled.

Lastly, the scientific evidence already present in the literature regarding the most frequent mutations investigated during clinical practice was confirmed.[15] In particular, in patients found to be positive for the IDH1 gene mutation, the median survival was 15 months, *i.e.* longer than the median survival found in overall patients. As indicated in the Sharma *et al.* (2021)[7] and Millward *et al.* (2016)[16] works, increased survival was also confirmed in patients with positivity for the IDH1 gene mutation and MGMT gene methylation. In patients in whom this combination was found, the median survival was 15 months. This subgroup includes the single subject with the highest survival observed in the sample, but with a diagnosis of oligodendroglioma, which is generally associated with a less inauspicious prognosis.

The most significant limitation of this work is the description of preliminary results only by statistical descriptive analysis, as enrolment has not yet been completed.

Conclusions

This study will provide the framework for increasing scientific knowledge in this area and for developing future prospective studies. Preliminary analyses aimed to show the distribution of high-grade glioma diagnoses in the Alessandria province.

These preliminary results presented and discussed confirmed scientific evidence already present in the literature. Analyses carried out to arrive at an initial geographical mapping of the distribution of diagnoses of high-grade gliomas are consistent in relation to the population density of each municipality examined. The hypotheses on the incidence of diagnoses in some municipalities with lower population density will be proposed again, and discussed again, in the final statistical analysis. The data obtained in this first part of the project provide the basis for future statistical analyses, using the georeferencing method, aimed at searching for the presence of possible clusters in a specific area/region of the Alessandria province.

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