DIFFUSE PONTINE INTRINSIC GLIOMAS: FIRST REGISTRY EFFORT IN MEXICO

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Abstract

Introduction: Brain tumors in children are the main cause of cancer related death in the pediatric population. Brainstem tumors incidence comprises 10.9% of all brain tumors having the Pediatric Diffuse Intrinsic Pontine Gliomas (DIPG) a fatal prognosis. Some countries have developed a national and international register database, to characterize their population. This study provides a retrospective population-based data to describe the epidemiology of children with DIPG in México from 2001-2021, and assesses the proposed prognostic factors previously described for survival outcome. Methods: Health Institutions from México were invited to fill in a retrospective registry of DIPG patients. Epidemiological, clinical, diagnostic, histopathologic and treatment variables were described. Fisher exact test was used to compare long, and short-term survivors and overall survival was estimated using the Kaplan-Meier Method. Differences between survival curves were evaluated using the Log-rank test and Cox proportional hazards regression analysis. Results: One-hundred and ten patients were included in the analysis. Median age at diagnosis was 7 years. Sixty patients (54.5%) presented with symptoms in less than 6 months being the most frequent ataxia (56.4%). Treatment was offered to 90 patients (81.8%), overall survival at 160 weeks (4 years) was 11.4%, and 16 patients (14.5%) arrived at clinical centers to die. We found no significant survival differences in any of the prognostic factors. Conclusion: This study highlights the need to develop improvement strategies to streamline healthcare processes and enhance quality of care to strengthen our situational diagnosis in Mexico.

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DPIG	Diffuse pontine intrinsic glioma
OS	Overall survival
EFS	Event free survival
SIOPE	Société Internationale d'Oncologie Pédiatrique Europe (International Society of Pediatric Oncology Europe)
PET/CT	Positron emission tomography/computed tomography
MRI	Magnetic resonance image

TITLE

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ABSTRACT (240 words)

Introduction: Brain tumors in children are the main cause of cancer related death in the pediatric population. Brainstem tumors incidence comprises 10.9% of all brain tumors having the Pediatric Diffuse Intrinsic Pontine Gliomas (DIPG) a fatal prognosis. Some countries have developed a national and international register database, to characterize their population. This study provides a retrospective population-based data to describe the epidemiology of children with DIPG in México from 2001-2021, and assesses the proposed prognostic factors previously described for survival outcome.

Methods: Health Institutions from México were invited to fill in a retrospective registry of DIPG patients. Epidemiological, clinical, diagnostic, histopathologic and treatment variables were described. Fisher exact test was used to compare long, and short-term survivors and overall survival was estimated using the Kaplan-Meier Method. Differences between survival curves were evaluated using the Log-rank test and Cox proportional hazards regression analysis.

Results: One-hundred and ten patients were included in the analysis. Median age at diagnosis was 7 years. Sixty patients (54.5%) presented with symptoms in less than 6 months being the most frequent ataxia (56.4%). Treatment was offered to 90 patients (81.8%), overall survival at 160 weeks (4 years) was 11.4%, and 16 patients (14.5%) arrived at clinical centers to die. We found no significant survival differences in any of the prognostic factors.

Conclusion: This study highlights the need to develop improvement strategies to streamline healthcare processes and enhance quality of care to strengthen our situational diagnosis in Mexico.

MAIN TEXT (2751 words)

Introduction

Brain tumors in children are the main cause of cancer related death in the pediatric population. The overall incidence of brain tumors is around 23.41 per 100 000 population in the United States, and 6.06 per 100,000 population among children and adolescents aged 0-19 years[1]. Brainstem tumors incidence comprises 10.9% of all brain tumors in this population. Pediatric Diffuse Intrinsic Pontine Gliomas (DIPG) is a malignant brain tumor with a median overall survival of 9 months[2]. Symptoms appear in a short time, and include cranial nerve involvement, long tract signs and cerebral deficits. A magnetic resonance imaging (MRI) with and without gadolinium administration is the study of choice and can confirm the diagnosis when biopsy is not possible due to the anatomical location and high morbidity rate associated with the procedure. Actual therapeutic strategies include radiotherapy with or without chemotherapy with a palliative care approach and only a few months of increase insurvival[3]. Treatment strategies have not improved survival and since DIPG is a rare tumor, non-randomized trials with a low number of patients constitute most of the available information. Some countries have developed national and international register databases of pediatric patients with DIPG. In 2011, the International Society of Pediatric Oncology Europe (SIOPE) formed the SIOP DIPG Network to create an online resource of comprehensive data on DIPG patients to initiate collaborative clinical trials with uniform criteria and share information on diagnosis, treatment, ongoing clinical trials, and additional care for DIPG patients[4]. From these data base registries, some characteristics, both clinical and radiological, have become possible prognostic factors for survival, including duration of symptoms prior to diagnosis for more than 12 months, age less than 3 years at diagnosis, use of chemotherapy, and the presence of ring-enhancement on MRI as an unfavorable factor[5]. These predictors have been validated in a SIOP DIPG Registry cohort[6].

End of life care is complex for patients with DIPG, requiring surgical procedures and other medical treatments to minimize or alleviate symptoms like pain, seizures, dysphagia, constipation, or urinary retention, and to make everyday tasks easier for their families. Most families still pursue chemotherapy treatment to improve quality of life. Planning the place of death is also important to all families with children with DIPG[7].

The availability of tumor tissue for accurate diagnosis and research purposes is a difficult task due to anatomical location or tumor size at diagnosis. Routine tumor biopsy is still under debate, considering diagnosis can be made with radiological studies[8], and it is recommended before treatment if molecular targeted therapies are planned under a clinical trial[9]. The collection of post-mortem tumor tissue can be an alternate approach to understand the biology of this group of tumors, but autopsies cannot always be performed. Families must consent for a brain autopsy and pathologists need to include unfixed brain tissue for molecular studies[10]. An informed consent for research analysis must be signed as well. These procedures are not always possible to achieve if the patient dies at home.

With some difficulties due to lack of registries in the past, Mexico has worked to establish a national registry. In 2016, a group of pediatric oncologists reported a significant number of patients with brainstem gliomas, where the main symptom was ataxia and the overall survival at 5 years was 68%. All patients with DIPG died[11].

The purpose of this study is to provide a retrospective population-based data to characterize the descriptive epidemiology of children with DIPG in México from 2001-2021, and assess proposed prognostic factors

previously described for survival outcomes.

Methods

Health Institutions from Mexico were invited to fill in a retrospective registry of patients with DIPG. All patients were included. The study was approved by the Institutional Review Board of six institutions. Demographic variables included, age, sex, duration of before admission, clinical signs at admission, image studies for diagnosis and treatment. Histopathological diagnosis and type of surgery was described when available. Overall Survival (OS) was defined as the time from diagnosis to death or last follow-up. Survival at 9 and 12 months was calculated. The value of 9 and 12 months was chosen as an arbitrary cutoff considering the average survival of DIPG patients, and the cut-off chosen at clinical trials. Short-term survivors were defined as those with an OS <12 months and long-term survivors as those with an OS of >12 months.

Patients' demographic, clinical and diagnostic characteristics and treatment variables were summarized using frequencies and percentages or median ranges. Cause of death or palliative care treatment was described when available. Fisher's exact test was used to compare long, and short-term survivors and OS was estimated using the Kaplan-Meier estimate. Differences between survival curves were evaluated using the Log-rank test with a P-value < 0.05 indicating a significant difference. Also, the Cox proportional hazards regression analysis was performed for univariate and multivariate hazard ratios for all variables of interest.

Prognostic variables used for survival were age (cutoff at 3 years), duration of symptoms at diagnosis (cutoff at 6 months), and chemotherapy plus radiotherapy at any time during the disease course. Radiological data on diagnostic imaging was not used due to missing data.

All statistical tests were performed using SPSS, version 25 (IBM Corp- Released 2017. IBM SPSS Statistics for Mac, Armonk, NY: IBM Corp)

Results

Twenty-three institutions that are members of the Mexican Agrupation of Pediatric Hemato-Oncology were invited to participate in a survey. The survey consisted of a database with epidemiological information of patients with high-grade brainstem gliomas from 2001 to 2021. Six institutions answered the registry and submitted the protocol to the research and ethics committee. All patients with complete information were included. The health institutions that participated were the Instituto Nacional de Pediatría, Hospital Siglo XXI from the Instituto Mexicano del Seguro Social (IMSS), Centro Médico Nacional 20 de Noviembre, from the Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE), Hospital General de México Dr. Eduardo Liceaga from México City, and the Hospital CIMA from Sonora, México.

We analyzed 110 patients with DIPG (Table 1). Annual variations were observed; 14 patients were registered in 2014 and only 1 registered in 2003, 2006 and 2009.

Forty-seven patients (42.7%) were males, and 63 (57.3%) females. Median age at diagnosis was 7.0 years (1 – 17 years). Only 17 patients (15.5%) were 3 or less years old. The most frequent age at diagnosis was at 6 years with 16 patients, and 51 patients were diagnosed at 4-7 years (46.3%).

Sixty patients (54.5%) presented with symptoms in less than 6 months. Behavioral disturbances were reported in 8 patients, with somnolence and irritation being the most frequent. The most common clinical symptoms at diagnosis were paresis 31 (28.2%) and abnormal eye movement (diplopia) 25 (22.7%).

The most frequent signs reported were ataxia 62 (56.4%), cranial nerve palsies 57 (51.8%) with compromise of cranial nerve VI in 35 (31.8%), VII in 32 (29.1%), III in 25 (22.7%) and IV in 14 (12.7%). Other signs reported were facial asymmetry 32 (29.1%), dysmetria 17 (15.5%), hyperreflexia 24 (21.8%), the Babinsky sign in 18 (16.4%) and hemiplegia in 28 (25.5%). Hydrocephalus was present in 37 patients (33.6%) and 24 (21.8%) received a shunt.

Spectroscopy was available in 22 patients (20%) and positron emission tomography/computed tomography (PET-CT) in 6 (5.5%). Tomography was used for initial diagnosis in 74 (67.3%) and magnetic resonance

image was used to complete it in 100 (90.9%). Descriptive image diagnosis was not available in all patients.

Ninety patients (81.8%) received treatment. Radiotherapy was reported in 76 (69.1%). Among these patients, the total dose used was 54 Gy (49.1%) followed by 55 Gy and 50.4 Gy (10% each). Of these 76 patients, 35 (31.8%) underwent normofractioned radiotherapy.

Histological diagnosis was available in 58 patients (52.7%), 3 of whom (2.7%) were not conclusive and 1 (0.9%) was unknown. The most frequent diagnosis was pilocytic astrocytoma 19 (17.3%) and anaplastic astrocytoma 15 (13.6%). Chemotherapy was used in 67 patients (60.9%), being concomitant with radiotherapy in 36 (32.7%), neoadjuvant in 9 (8.2%) and adjuvant in 22 (20%). Steroids were used in 44 patients (40%).

Surgery performed to ameliorate symptoms or to improve quality of life were shunt 24 (21.8%), gastrostomy 15 (13.6%), tracheostomy 7 (6.4%) and port-catheter 8 (6.3%).

Ten patients survived (9.1%) and the longest survivor was reported at 16 years from diagnosis, 90 patients (81.8%) died, and 10 (9%) were lost to follow-up. Considering the cutoff points of 9 and 12 months, 72 patients (65.5%) patients died in less than 9 months and 79.1% in less than 12 months. Thirty patients died at home (27.3%) and 28 at the hospital (25.5%). Only 2 (1.8%) autopsies were performed. Palliative care was given in 22 patients (20%). Only 88 patients had a complete registry to determine survival. Of these 88 patients, overall survival was 11.4% and event free survival was 19.3% at 160 weeks (4 years) (Fig 1). Sixteen patients (14.5%) died at medical centers at diagnosis, and 33 (30%) died within one month of diagnosis

Progression was documented with an image report in 40 patients (36.4%). Only 50 patients had a date of death. Median time to death was 172.32 days (range 0-3660).

There was no significant survival difference (PFS or OS) according to the 3 years of age cutoff (Log-rank PFS p=0.310 and OS p=0.399), oncologic treatment (Log-rank PFS p=0.523 and OS p=0.679), or steroids use (Log-rank PFS p=0.384 and OS p=0.462). There was a significant difference in PFS between sexes but not with OS (Log-rank PFS p=0.035 and OS p=0.091).

Fisher's exact test was used to compare long and short-term survivors in terms of certain variables of interest. Accordingly, hyperreflexia, onset of symptoms in less than six months, and use of radiotherapy with concomitant radiotherapy differed significantly (p= 0.028, p= 0.009 and p=0.007, respectively). According to our logistic regression analysis on these variables, the best model to predict survival was hyperreflexia and radiotherapy with concomitant chemotherapy (p= 0.001) where hyperreflexia and concomitant treatment had a protector prognostic factor (OR 0.225 p=0.012 (95%CI 0.070-0.720) and OR 0.231 p=0.009 (95%CI 0.077-0.690) respectively). Onset of symptoms in less than six months showed no significance between the groups (p= 0.061)

A Cox proportional hazards regression analysis was performed for univariate and multivariate hazard ratios without any significance for all variables of interest. Considering the 3 rears of age cutoff, onset of symptoms in less than six months or concomitant treatment showed no significance (p= 0.888).

Discussion

The prognosis for children with DIPG has remained dismal. The low incidence of these tumors makes clinical trials hard to perform and data from different health institutions and countries are difficult to compare due to a lack of consensus in inclusion, exclusion, and response criteria. Another issue is the number of specialists who care for these patients. Pediatric oncologists, neurosurgeons, neurologists, emergency doctors and pediatricians are an important part of a large team of specialists. Considering treatments, new pharmacological strategies are used randomly without randomized controlled clinical trials. Historically, another variable is the possibility of performing a tumor biopsy and neurosurgeons' criteria for a tumor biopsy. This surgical limitation has resulted in lack of knowledge on the histology and malignancy grade of tumors, forcing medical doctor to sometimes overtreat some patients. The variability of access to medical attention, differences in patient and family care choices, performance of the surgery, classification of disease risk, indication of radiotherapy, decision to start palliative care, and magnitude of medical and surgical interventions to give

nutritional support or to avoid intracranial hypertension among other issues have made the medical approach to this problematic disease very heterogeneous. Hence, it has become difficult to come to a consensus and establish standardized diagnostic and treatment strategies[12].

In 2011, the International Society of Pediatric Oncology in Europe (SIOPE) created a DIPG Registry with the aim to collect epidemiological, clinical, diagnostic, histopathological, treatment, and prognosis data to allow collaborative and structured analysis studies among every participating country[4].

Mexico is one of the countries participating in this DIPG Registry. The first section of this registry is a retrospective analysis and the second a prospective inclusion of new cases. Our aim was at first to start a collaborative initiative in Mexico for a registry based on the International DIPG Registry. As a second point, we made a situational diagnosis of patients' clinical characteristics and quality of clinical care and analyzed the Mexican hospitals that participated. The analysis of signs and symptoms at diagnosis match with the epidemiological data reported in other countries[13, 14, 15, 16]. Some interesting data from our cohort is that 45.5% of patients are diagnosed after six months, which may not change the final prognosis but could delay symptom relief. We report 9.1% of the patients survived and one of these patients was 16 years old at the time of this report. Considering the median time to survival, 65.5% of the patients died in less than 9 months.

Considering the parameters for quality of standard care, we found that almost 90% of patients were diagnosed with a magnetic resonance image and only 20% with spectroscopy. Though the conventional use of magnetic resonance imaging over computed tomography has become the standard method of diagnosis, many health institutions have still not made further use of spectroscopy or other new techniques due to availability, where patients must travel in delicate conditions to get one[17]. Six patients had a PET-CT which is not a standard tool, and we documented these cases were not in a research protocol. Interestingly, tumor tissue was available in almost half of the patients, but no molecular studies were performed. This is a very important point in which neurosurgery has the surgical skill and attitude to take oriented decisions. Even if molecular studies are not available, discriminating between low and high-grade cases is fundamental for understanding the clinical course and considering the use of chemotherapy in a reasoned way.

Treatment with radiotherapy was used in 91 patients, which makes a standpoint observation because it is at this moment the standard option of treatment. Some patients could not receive it because they arrived at a hospital and died in the first week after diagnosis. Use of steroids as part of initial treatment was observed in 40 patients, which elucidates that not all health centers use them as part of their treatment, as it has been documented that side effects can be important, and the health benefits and risks remain controversial[18].

Only a small proportion of patients were evaluated by a palliative care team, and some were treated with a gastrostomy and/or tracheostomy as part of end-of-life care. However, no information was available on the use, type, or dose of steroids and pain treatment in any of the patients. Not all hospitals have a palliative care team, or end-of-life guidelines for pediatric patients with DIPG; the initial treatment is given by the oncology department. There is still scarce information about what specific special needs are appropriate for palliative and end-of-life care in these patients[19, 20].

Two autopsies were performed, though 16 patients died at a hospital. Collecting postmortem tumor tissue can be of great importance in countries like ours where molecular analysis cannot always be performed, to begin understanding, along with tumor tissue from alive patients, histopathology, and immunochemistry patterns[21].

Our study has several strengths and limitations. The strengths include the national collaboration, and effort to show and understand a partial situational diagnosis of the country in the DIPG problem, its diagnosis, and treatment strategies, as well as standard of end-of-life care. Latin America has not gathered information on DIPG pediatric patients to date. The main limitation was the lack of national collaboration. This is such an issue that the Mexican Society of Pediatric Onco-Hematology is working on it through clinical research courses and presentation of initiatives among other things.

This study highlights the need to develop improvement strategies to streamline healthcare processes and improve quality of care in DIPG. We could not perform multivariate analysis due to the number of patients studied and the lack of information available. Further research must be done to show data that can be compared to international patient series. Still, in our country, not all risk factors can be measured, collected, analyzed, and compared with high-income countries; therefore, we may need to adapt other clinical, diagnostic and treatment related factors to our population. Still, as members of the SIOPE Registry for patients with DIPG, the repository and description of images are of great importance and must be applied to our database as a prospective goal, along with the molecular analysis of tumor tissue and standard of treatment care.

Conflict of Interest statement

There is no conflict of interest by any of the authors in this manuscript

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TABLES

TABLE 1: Patient characteristics

Demographic / Clinical	n = 110
Age, (median in years)	7y?¿?
3 años	17
Gender, male	47
Symptom duration prior to presentation	
< 6 weeks	60
6-12 weeks	11
12-24 weeks	12
>24 weeks	6
Unknown	21
Symptoms and signs at presentation	
Conduct alterations	8
Ataxia	62
Hemiplegia	28
Quadriplegia	5
Dysmetria	17
Diplopia	25
Babinski	18
Papilledema	3
Cranial nerve palsy	57
Hydrocephalus	37
Diagnosis corroborated with imaging	
Magnetic Resonance	100
Tomography	74

Demographic / Clinical	n = 110
Spectroscopy	22
Treatment	90
Surgery (biopsy)	58
Radiotherapy	76
Chemotherapy	67
Neoadjuvant	9
Concomitant	36
Adjuvant	22
Steroids	44
Progression by image	40
Patient alive at 9 months	38
Place of death	
Hospital	28
Other	2
Home	30
Unknown	50
Autopsy	2
Palliative care	22

FIGURES:

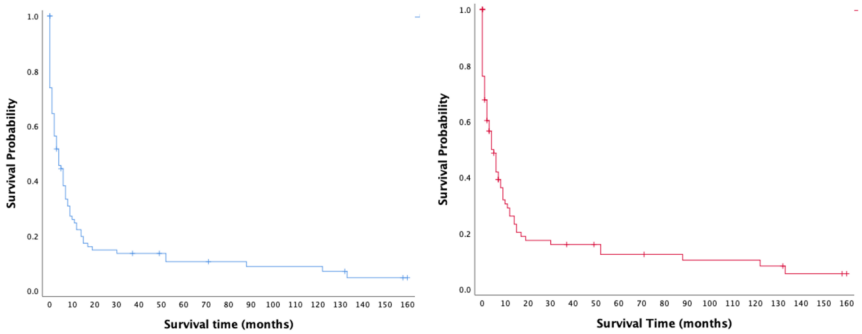

Fig 1. Overall survival (OS) and Event free Survival (EFS) for the entire cohort. Blue line represents OS, red line represents EFS

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