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Clinical and epidemiologic characterization and follow-up of children with central nervous system tumors

Caracterización clínica-epidemiológica y seguimiento de niños con tumores del sistema nervioso central

Jorge Dornellys da Silva Lapa[1], Rilton Marcus Morais[2], Leyla Manoella Maurício Rodrigues de Lima[3], Carlos Umberto Pereira[4], Thais Melo[5], Rosana Cipolotti[5]
Universidade Federal de Sergipe, Aracaju SE, Brasil.

1 MD, Residente em Neurocirugia da Fundação Beneficente Hospital Cirurgia (FBHC), Aracaju, SE.
2 MD, Neurocirurgião, Serviço de Neurocirurgia Pediátrica do Hospital de Urgência de Sergipe, Aracaju SE, Brasil.
3 MD, Residente em Pediatria, Hospital Universitário da UFS, Aracaju SE, Brasil.
4 MD, PHD, Preceptor da residência em neurocirurgia na FBHC, Aracaju, SE.
5 Acadêmica em Medicina na Universidade Federal de Sergipe (UFS), Aracaju, SE, Brasil.
6 MD, PhD, Professora Associada de Pediatria, Departamento de Medicina, UFS, Aracaju SE, Brasil.

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Resumen

Objetivo: Evaluar distribución, presentación clínica inicial y tasa de supervivencia de los niños con tumores del sistema nervioso central tratados en capital de la región nordeste de Brasil. **Método**: Estudio prospectivo que involucra a pacientes menores de 19 años admitidos entre julio/2011 y julio/2013. **Resultados**: La incidencia media anual aproximada de tumores pediátricos del SNC en Sergipe fue de 22,4 casos por cada 1.000.000 niños y adolescentes por año. El promedio de edad fue 7,68 años, siendo el 67,6% de pacientes del sexo femenino y el 76,5% de no blancos. La cefalea y los vómitos estuvieron presentes en la admisión en el 79,4%, en su mayoría con déficits neurológicos. El cerebelo fue la estructura anatómica más afectada (32,4%). La localización infratentorial fue observada en el 50% de los casos. Las morbilidades asociadas fueron más frecuentes en el compartimiento supratentorial (p = 0,015) y las categorías histológicas más frecuentes fueron astrocitoma pilocítico (23,5%), glioma difuso de puente (17,6%) y 11,8% meduloblastoma, craneofaringioma, ependimoma, cada uno. La resección quirúrgica fue posible en el 70,5% de los casos, en la mayoría sin terapia adyuvante. La supervivencia después de 12 meses fue el 72,8% y después de 24 meses, el 37%. **Conclusión**: La muestra posee características demográficas, histopatológicas, clínicas y supervivencia a 12 meses semejantes a la literatura. La caída de la supervivencia a los 24 meses puede reflejar la participación de los tumores de tronco encontrados en nuestra muestra.

Palabras clave: Sistema nervioso central, neoplasias, niño, supervivencia.

Abstract

Objective: To evaluate distribution, initial clinical presentation and survival rate of children with central nervous system tumors treated in a capital city of Northeast, Brazil. **Method**: This is a prospective study, which includes patients aged under 19 years admitted between July/2011 and July/2013. **Results**: The approximate mean annual incidence of pediatric CNS tumors in Sergipe was 22.4 cases per 1,000,000 children and adolescents per year. The mean age was 7.68 years, 67.6% were female and 76.5% non-whites. In 79.4%, headache and vomiting were present at first clinical evaluation, in the majority associate with neurological deficits. The cerebellum was the most affected anatomic structure (32.4%). The infratentorial compartment was compromised in 50% of cases. Associated morbidities were more frequent in the supratentorial compartment (p = 0.015) and the most frequent histological types were pilocytic astrocytoma (23.5%), diffuse intrinsic pontine glioma (17.6%) and 11,8% medulloblastoma, craniopharyngioma, ependymoma, each. Surgical resection was possible in 70.5% of cases, mostly without adjuvant therapy. A 12-month survival rate was 72.8% and a 24-month survival rate, 37%. **Conclusion**: Our sample has

demographic, histopathological, clinical and a 12-month survival rate similar to other studies. The decrease in the 24-month survival rate may be due to brain stem tumors found on our sample.

Key words: central nervous system, cancer, child, survival.

Introduction

Primary tumors of the central nervous system (CNS) are the second most frequent tumor in pediatric patients, the first being those with oncohematologic origin[1]. However, mortality due to CNS tumors is the highest of the pediatric tumors[14]. The incidence has increased in the past decades, mainly due to innovations in the imaging studies, with the increase of diagnoses of benign forms[3].
Clinical manifestations of pediatric CNS tumors are variable in relation to location, age, infiltrative or mass effect behavior, with the most common histologies, with decreasing frequency, astrocytomas, medulloblastomas and craniopharyngioma[3].
There is an important variation in survival rates, depending on the histological type of the tumor, however, with the improvement in surgical techniques, there was a reduction in the mortality rates of resectable tumors, even though with high levels of neurological impairment[15].
A population-based cancer registry in Aracaju, capital of Sergipe, identified lower cases than recorded in a hospital database in the same city, which motivated this prospective study. It is a clinical, epidemiological, histopathological and prognostic profile of pediatric patients with primary CNS tumors attended at Sergipe's only public pediatric neuro-oncology service, which therefore reflects the profile of the disease in the state[11].

Methods

A prospective study was conducted with children and adolescents with CNS cancer, accompanied at the Pediatric Oncology Service of the Osvaldo Leite Oncology Center, the only reference of the Unified Health System in the state of Sergipe for oncological neurosurgery, which also serves the north of Bahia and the Alagoas border. Correlations among clinical data, results of imaging tests and biopsies, as well as response to treatment modalities were evaluated.
All infants and adolescents until the age of incomplete 19 years old, with a confirmed diagnosis of primary CNS tumor of both sexes from July 2011 to July 2013 were eligible for the study.
The project was approved by the Research Ethics Committee on Human Beings of the Federal University of Sergipe. The patients and their caregivers were clarified by the researcher about the objectives of the research, and those who agreed to participate signed a Free and Informed Consent Term (FICT). The patients were evaluated in the scheduled appointments and/or periods of hospitalization. The data were obtained from the patient's evaluation through a form, with emphasis on initial complaints, alterations of the neurological examination, as well as imaging and pathology exams. The therapeutic modalities were defined by the oncologist responsible for the case, and the information regarding treatment, survival and intercurrences were obtained from the medical records and information collected from these oncologists.
Continuous variables were expressed as mean, standard deviation, median and range, and proportional variables were expressed in absolute numbers and absolute and relative frequencies. The incidence of the various types of CNS tumors in the state of Sergipe was estimated. The survival estimate was calculated using the Kaplan-Meier performance curve, using the statistical program SPSS version 17.0. Associations were assessed using Fisher's exact test and differences between groups were considered significant with a "p" value < 0.05.

Results

Thirty-six patients with clinicopathological lesions compatible with CNS tumors were evaluated, excluding two, due to histopathology compatible with vascular malformation. The mean age was 7.68 years (SD: 4.16), 67.6% of which were female patients. The majority of the patients are non-white (76.5%), with an average family income of 1.7 minimum salaries (SD: 1.33), 26.5% of which were from the states of Bahia and Alagoas.
One of the patients had a phacomatosis, tuberous sclerosis, and 20.6% had a family history of neurological disease (epilepsy).
Headache and vomiting were present in 79.3% of the patients at presentation, but in 29.3% of the patients there were no alterations to the neurological examination, although headache in those cases is characteristically irresponsive to usual medications. The most common associated neurological changes, in descending order of frequency, were diplopia, visual acuity decrease and gait instability. In both patients under one year old, the clinic presented as inconsolable crying, vomiting and a bulging anterior fontanelle (Table 1). The duration of symptoms until diagnosis was on average 3.23 months (SD: 6.20).
The infratentorial compartment was involved in 50% of the tumors, there was a tumor located in the intradural space and two tumors with both supratentorial and infratentorial extension. The highest proportion of deaths occurred in patients with tumors in the infratentorial compartment. The cerebellum was the most affected anatomic structure (32.4%), followed by the brainstem with 23.5%, the sellar region with 17.6% and the pineal region with 8.8%. The most common histologies were pilocytic astrocytoma (23.5%), diffuse glioma in pons (17.6%), medulloblastoma, craniopharyngioma and ependymoma with 11.8% (Table 2).
The approximate mean annual incidence of pediatric CNS tumors in Sergipe was 22.4 cases per 1,000,000 children and adolescents per year, using the 2010 census data, with th pilocytic astrocytomas being the most frequent tumors counting with 5.25 Cases per million, followed by brainstem glioma, with 3.95 cases per million, in addition to craniopharyngioma, medulloblastoma and ependymoma with 1.97 cases

Table 1.
Admission symptoms of pediatric CNS tumor patients treated at the pediatric oncology service associated with HUSE

Admission symptoms	Absolute freqeuncy	Percentage (%)
Headache and vomiting	10	29,3
Headache, vomiting and diplopia	6	17,6
Headache, vomiting and visual disturbance	5	14,7
Headache, vomiting and gait instability	4	11,8
Seizures	2	5,9
Labial commissure deviation	2	5,9
Bulging anterior fontanelle, vomiting	2	5,9
Headache, vomiting and strength chance	2	5,9
Torticollis and strength chance	1	2,9
Total	34	100

Table 2.
Distribution of frequencies of pediatric CNS tumors by histopathology results

Histology	Absolute Frequency	Percentage (%)
Medulloblastoma	4	11,8
Craniopharyngioma	4	11,8
Ependymoma	4	11,8
Brainstem glioma	6	17,6
Germinoma	1	2,9
Pilocytic Astrocytoma	8	23,5
Papilloma	1	2,9
Pineocytoma	2	5,9
Pineoblastoma	1	2,9
Neurofibroma	1	2,9
Oligodendroglioma	2	5,9
Total	34	100

per million each. A curative surgery, which intents the complete tumor removal, was available in 70.5% of the cases, and in 62.5% of this subgroup did no need for chemotherapy or adjuvant radiotherapy. The ventricularperitoneal shunt (VPS) procedure, as an emergency measure or as a palliative measure, was performed in 52.9% of the patients. Adjuvant therapies were applied in 52.9% of all patients.

It was observed a frequency of 26% for associated morbidities following the patients whose tumors were treated with potentially curative therapies. By the direct presence of the tumor or due to surgery or placement of Omaya catheter for intratumoral chemotherapy in craniopharyngiomas, the most common changes were hypopituitarism and muscular strength pattern. Associated morbidities were more frequent in the supratentorial compartment ($p = 0.015$).

During follow-up, tumor recurrence was observed in 31.8% of patients who had presented with remission disease by imaging criteria, after surgery or intratumoral chemotherapy.

After two years of study, 70.6% of enrolled patients were alive, with variable length of follow-up. Survival estimates, using the Kaplan-Meier curve, showed that after 12 months of follow-up, survival was 72.8% and after 24 months, 37%. (Figure 1). The estimated survival rate for pilocytic astrocytoma was 100% at 12 months, whereas for brainstem tumors it was 33%, with a mean survival time of 11.7 months (SD = 1.20).

Discussion

The most affected group of CNS tumors, in the present study, was school children, similar to the literature, with typical symptoms for approximately three months before diagnosis[2]. The predominance of nonwhites, a possible result of Brazilian miscegenation, contrasts with international publications which the predominant population is Caucasian[13]. The frequency of female children and adolescents was higher, which differs from other authors[4].

The average family income was less than two minimum salaries and it reflects the socioeconomic level of the patients served by the service.

The considerable number of patients residing in other states, who were taken care in the service, may be associated with the shorter distance from these cities in the interior of Bahia and from Alagoas to Aracaju, in relation to their respective capitals and larger cities.

Considering the pathological antecedents of the patients, it was observed that one of them had previous diagnosis of tuberous sclerosis. Tuberous sclerosis is a genetic disease with cutaneous and nervous system involvement, with characteristic clinical features, but with low incidence[12].

The clinic associated with pediatric CNS tumors is related to the age of the patient and the location of the tumor[9]. The clinical manifestations mentioned were similar to the literature, with headache and vomiting not responding to usual medications, as part of the intracranial hypertension syndrome, the most common symptoms[16]. It was observed in most cases that headache and vomiting started the symptoms and they were associated with objective changes in neurological examination (63%), especially in older children.

The infratentorial compartment was the most frequently affected (50%), which is compatible with previous results[2]. Also, the infratentorial location had a higher proportion of deaths with a percentage of 33.3%. There was a single

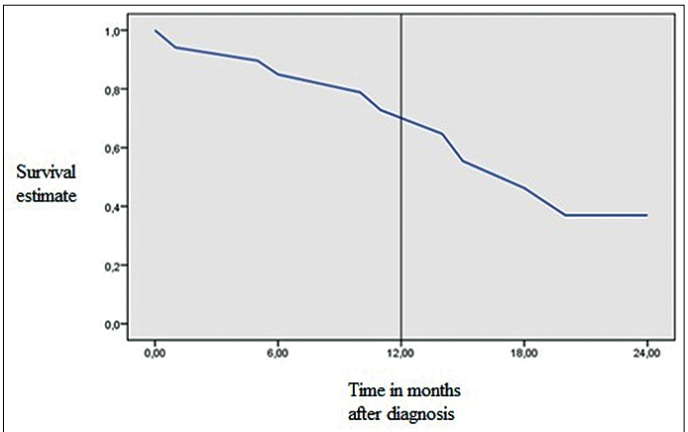

Figure 1. Survival of pediatric patients with CNS tumor after 24 months of follow-up.

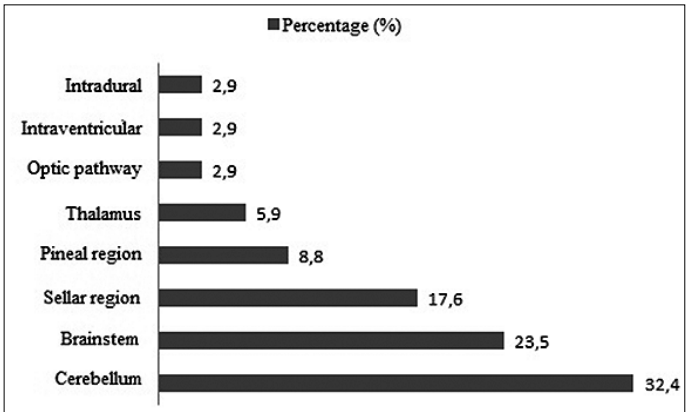

Figure 2. Distribution of frequencies of pediatric CNS tumors by the anatomical structure initially affected.

case where the tumor was located in the high cervical spine, different from the thoracic spine location, identified as the most common. In this case, the tumor was intradural, but extramedullary, diverging from the literature, in which shows intramedullary tumors[17].

The most common histopathological category was pilocytic astrocytoma (23.5%), equivalent to the 35% in the literature as the most common histopathology[2]. However, brainstem glioma was the second most common histological type (17.6%), which diverges from a classic study on the subject, which shows the medulloblastoma in the second position. In general, the most common histologies of international studies were represented in this study (craniopharyngioma, ependymoma and medulloblastoma). The initial involvement of anatomical structures followed the same pattern of Ramanan and Chaseling (2012), the posterior fossa being subdivided in the present study, showing the cerebellum as the most affected site, followed closely by the brainstem (Figure 2)[10].

The mean annual incidence of pediatric CNS tumors in Sergipe was close to the average of 27.4 to 30.94 cases per million from population-based studies in Brazil. The incidence determination by histopathology contributes to the planning of the necessary inputs for diagnosis and therapy of each specific type of tumor[7].

Therapeutic surgery was performed in 70.5% of the cases, and in 62.5% of these there was no indication of adjuvant therapy, which is above the 50% found in a large study. The VPS use frequency in this study (52.9%), performed to control hydrocephalus, was very similar to that of the study by Wong et al (2011), which was 56.7%[18].

More than a quarter of the patients with potentially curative treatments had some associated morbidity at follow-up, such as motor or hormonal deficits, the most observed alterations were in the supratentorial compartment[6,15]. In addition, overall survival after 12 months was 72.8%, below the 89% found by Ramanan and Chaseling (2012) and slightly higher than the 67% observed in another study in the northeast of Brazil[1]. However, at 24 months, the survival estimate was 37%, much lower than the 52% found in the study[1]. A possible explanation for an abrupt reduction in survival after 12 months may be associated with a higher average of brainstem glioma survival in this study, which is above the 8-month mean of De Araujo (2011), shifting the impact of mortality by brainstem gliomas for the second year of follow-up[1]. Moreover, this higher survival rate may be related to the quality of the palliative care service. In addition, one possibility to modify the low survival of brainstem gliomas could be the use of stereotactic biopsy, which is considered a safe procedure and could better stratify these tumors, allowing more targeted therapy[5,8].

It is concluded that the sample studied has demographic characteristics similar to those reported in other studies, as well as the distribution by histological type and the survival rate at 12 months. The drop in survival rate at 24 months may at least partially reflects the involvement of brainstem tumors.

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Correspondência:
Jorge Dornellys da Silva Lapa
Rua Roque José de Souza, nº 116, Campo do Brito/SE, Brasil CEP: 49520-000
dr.dornellys@hotmail.com