ORIGINAL ARTICLE

EXPERIENCE IN DIAGNOSTIC AND TREATMENT OF CENTRAL NERVOUS SYSTEM TUMORS IN CHILDREN LESS THAN 2 YEARS AT THE BACA ORTIZ PEDIATRIC HOSPITAL, QUITO-ECUADOR, 2016-2019

Experiencia en el diagnóstico y tratamiento de tumores del sistema nervioso central en niños menores de 2 años en el Hospital pediátrico Baca Ortiz, Quito-Ecuador, 2016-2019

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ABSTRACT

Introduction: Tumors of the central nervous system (CNS) in children between 0 and 2 years of age are infrequent, so their diagnosis and treatment constitute an important challenge for every pediatric neurosurgical center, to which is added the comorbidities typical of this age that condition the responsibility of improving therapeutics to obtain better survival. The objective of this study was to describe the diagnostic and therapeutic experience of a neurosurgical Department of national reference, in relation to neoplasms of the central nervous system in children under two years of age, as well as to establish comorbidity and prognosis.
Methods: Cross-sectional, retrospective and descriptive study that includes all patients under 2 years of age who were diagnosed with a neoplastic lesion of the central nervous system, attended from January 01, 2016 to July 01, 2019 at the Baca Ortiz Pediatric Hospital from the city of Quito in Ecuador.
Results: CNS tumors in children between 0 and 2 years old corresponded to 5.09%, with irritability being the most frequent reason for consultation with 62.5%. Also, 75% of the neoplasms were located at supratentorial level with a 1: 1 intra / extra-axial ratio. Neuroblastoma and choroid plexus tumors were the most frequent histopathological diagnoses. Mortality had a percentage of 50%.
Conclusions: CNS tumors in children between 0 and 2 years are not frequent, the location is predominantly supratentorial and the prognosis for life depends on the histopathological type. Radiation therapy is an option, although surgery for resection is the basis of treatment.

Keywords: *Central Nervous System Neoplasms, Comorbidity, Prognosis. (Source: MeSH NLM)*

RESUMEN

Introducción: Los tumores del sistema nervioso central (SNC) en niños de entre 0 y 2 años son poco frecuentes por lo que su diagnóstico y tratamiento constituyen un reto importante para todo centro neuroquirúrgico pediátrico, a lo cual se agrega las comorbilidades propias de esta edad que condicionan la responsabilidad de mejorar la terapéutica para obtener mejor sobrevida. El objetivo de este trabajo fue describir la experiencia diagnóstica y terapéutica de un servicio neuroquirúrgico de referencia nacional, en relación con las neoplasias del sistema nervioso central en niños menores de dos años, además de establecer la comorbilidad y el pronóstico.
Métodos: Estudio transversal, retrospectivo y descriptivo que comprende a todos los pacientes menores de 2 años que fueron diagnosticados con una lesión neoplásica del sistema nervioso central, atendidos desde el 01 de enero de 2016 hasta el 01 de julio de 2019 en el Hospital Pediátrico Baca Ortiz de la ciudad de Quito en Ecuador.
Resultados: Los tumores del SNC en niños de entre 0 y 2 años correspondieron al 5,09% siendo el motivo de consulta más frecuente la irritabilidad con 62,5%. El 75% de las neoplasias se ubicaron a nivel supratentorial con una relación 1:1 intra / extra-axial. El neuroblastoma y tumores de plexos coroideos fueron los diagnósticos histopatológicos más frecuentes. La mortalidad tuvo un porcentaje del 50%.
Conclusiones: Los tumores del SNC en niños de entre 0 y 2 años no son frecuentes, la localización es predominantemente supratentorial y el pronóstico de vida depende del tipo histopatológico. El tratamiento con radioterapia es una opción, aunque la cirugía con fines de resección constituye la base del tratamiento.

Palabras Claves: *Neoplasias del Sistema Nervioso Central, Comorbilidad, Pronóstico. (Fuente: DeCS Bireme)*

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Neoplasms of the central nervous system (CNS) have an incidence of 5.3 cases per 100,000 children (1-19 years) in countries that have a registry of tumor pathology. [1,3,15] Up to 10% of brain tumors occur in children younger than 1 year, constituting 20% to 25% of malignancies in children younger than 3 years and being the leading cause of death from malignancy in childhood and in children under 19 years of age; [1, 2, 10] Furthermore, this pathology is more frequent in children in developed countries than in developing countries. [5, 9]

In infants under two years of age, as well as in adolescents, tumors appear with equal frequency in the posterior fossa and at the supratentorial level. [11]; It is also described that about half of the tumors are astrocytomas, 15% ependymomas, between 16% and 25% medulloblastomas and between 4% and 16% are gliomas 1, this order of frequency varies according to the location of the neoplasms [5, 9].

Tumor behavior, evolution and prognosis largely depend on its histological type, the age of the patient and the susceptibility to surgical and / or complementary treatment.[1,5]; The pathophysiology of the development of neoplasms of the central nervous system is generally poorly understood [1, 5, 9, 16, 17] although associations with genetic factors are currently described in about 10% of cases and in the remaining 90% it is considered influenced by environmental and / or immune factors [5, 17]. The literature describes symptoms and signs that are often related to intracranial hypertension and that are suggestive of a neoplasm of the central nervous system [4, 18]. Macrocephaly, the classic Cushing triad , bulging fontanel, vomiting, eyes in the rising sun, afebrile seizures (focal and complex), cranial nerve involvement and neurological targeting are common and evident in young children. [1, 6, 9]

The clinical suspicion begins the diagnostic work that will be complemented with image examinations and later the histopathological analysis resulting from the tumor excision or biopsy of a lesion, as well as the genetic-molecular studies that in the future will become essential in the clinical management of the tumor pathology [1, 2] Resection can be diagnostic and curative in certain types of tumors (for example: supratentorial low-grade gliomas), however, there are limitations for the treatment of many others (posterior fossa tumors: medulloblastomas or diffuse gliomas of midline) [2].

The multimodal treatment, frequent in this type of tumors, has led to a current increase in survival, reaching up to approximately 70% at 5 years. [3]. Standard management of tumors includes surgery, chemotherapy and radiation (in children older than 3 years).), which is difficult to comply with in children under 2 years of age, due to the morphological and physiological characteristics of this age group, making the interventions potentially very invasive and / or toxic.[2,3,20] Late complications that may occur Taking into account the great physiological maturation of young infants, especially at the level of the nervous system, they include neurocognitive, endocrine, sensitive neurological, cardio- cerebral- vascular disorders, secondary malignant disease, as well as psychological and social disorders· [3, 19]

The risk of intellectual deterioration is present regardless of the complementary treatment modality and has been known for several decades.[4,20]

As patient survival has improved, the frequency with which neurocognitive impairment is evident during follow-up has also increased; comorbidity that has attracted interest in the study mainly in patients with posterior fossa tumors. [4, 13]

The knowledge of these side effects led to the performance of several studies that tested chemotherapy treatments to defer or avoid radiotherapy, the same that should be avoided whenever possible. [6, 9]. Complementary treatment in younger lactating patients that has been studied and that has achieved survival results between 30% and 70% at 5 years of follow-up, includes prolonged postoperative chemotherapy with or without delayed radiation, high-dose chemotherapy or in patients with relapses. [10]

Surgery for tumor resection in such young patients carries a high risk of morbidity and mortality; Although surgery may be well tolerated, the increased risk of complications and the need for reoperations are also not overlooked. [6, 20]

METHODS

A cross-sectional, retrospective and descriptive study was carried out in all patients younger than 2 years old who were diagnosed with a neoplastic CNS injury and who were treated from January 01, 2016 to July 01, 2019 at the Baca Ortiz Pediatric Hospital from the city of Quito in Ecuador.

We present information that was collected by the authors on the signs and symptoms, as well as the evolution time at the time of diagnosis, imaging studies with the main morphological characteristics of neoplastic lesions, their location, laterality, and contrast enhancement; as well as the results of neurophysiological studies prior to any intervention were also recorded.

The treatments were documented in each of the cases (surgical and non-surgical) as well as the initial diagnostic suspicion and the definitive histopathological result in the operated patients. A record was kept of the follow-up time, case outcome, survival and complications presented during and after treatment. All the variables were collected in a tabulating data sheet from the clinical records of the patients that are in the hospital file.

The objective of the present study is to describe the experience of a national reference neurosurgical service, obtained during three years and six months in relation to CNS malignancies in children younger than two years, in order to suggest suitable elements for the initial approach, describe the diagnostic process, specify procedures to be performed in the pre-surgical preparation and describe the complications during the diagnostic-therapeutic process, as well as review the literature regarding prognosis and survival in this group of patients.

The results are presented in distribution matrices of variables for their exposition in the present study.

TABLE 1: Clinical characteristics of pediatric patients operated on brain tumor at Baca Ortiz Pediatric Hospital, Quito-Ecuador. 2016-2019.

Patient	Age (months)	Sex	Clinical evolution (days)	Symptoms	Signs	Cranial nerves affected
1	11	Female	5	Irritability	Vomiting, seizures	III
2	17	Male	21	Irritability	Vomiting, nuchal rigidity stiffness, paraparesis 4/5	We
3	24	Male	7	Irritability	Ocular proptosis, conjunctival hyperemia	II, III
4	21	Male	90	Disruption of visual acuity	Ocular proptosis	II
5	9	Female	60	Altering consciousness	Swallowing disorder	IX, X
6	8	Male	15	None	Ocular proptosis	II, III
7	4	Female	30	Irritability	Vomiting, seizures	III
8	4	Male	30	Irritability	Macrocephaly	III, VIII

Source: Medical records, Baca Ortiz Pediatric Hospital. (Made by Flores C.)

RESULTS

Eight patients under 2 years of age with CNS tumors were found in the period studied (2016-2019), which corresponded to 5.09% of all patients treated with CNS malignancies during that period; 62.5% were male, the average age at diagnosis was 12.25 ± 7.59 months, and only 1 case had a significant pathological history (type I neurofibromatosis). An attempt was made to collect information regarding exposure to external factors, but the information could not be obtained from existing records.

Clinical findings

In relation to the clinical picture, the average time elapsed from the onset of symptoms to diagnosis was 32.25 ± 29.07 days, the most frequent reason for consultation was irritability (62.5%), followed by changes visual, alteration of consciousness (1 case each). The most frequently reported symptoms were vomiting and proptosis (37.5% each) and seizures (25%). Macrocephaly, alteration of the lower cranial nerves, motor disorders and paraparesis were also found; the most frequently affected cranial nerves were III (5 patients), II (3 patients) and less frequently the lower cranial nerves (VIII, IX and X). (Table 1)

Diagnosis

Simple tomography was the first examination carried out on all patients and with this, the diagnosis of brain tumor was confirmed. Later, a CT scan with contrast was also performed in all patients and an MRI in 50% of patients. Neurophysiological studies of evoked potentials are part of the panel of presurgical examinations and were performed in 62.5% of patients (alterations in visual potentials were found in 3 patients, 37.5%), alterations in the lemniscal pathway were observed in 2 cases (25%), 1 patient with alteration of the auditory pathway was found, as well as 1 with a normal result.

Imaging characteristics of tumor lesions

75% of the patients had single injuries, the rest were diagnosed with multiple injuries; 75% of the patients had supratentorial tumor lesions and only 2 of them were infratentorial. According to peripheral or central location, 50% were intra-axial and 50% extra-axial lesions. According to location, the lesions were: 2 intraventricular, 2 frontal-orbital, 2 located at the level of the pons, 1 cerebellar and 1 extracranial; According to laterality, 37.5% were central, 37.5% left and 25% right. (Table 2)

87.5% of the lesions had a solid appearance, the remaining 12.5% had a mixed appearance (solid / cystic). In 25% of the cases the lesion was homogeneous and there was contrast enhancement in 87.5% of the tumors; 62.5% of the lesions had associated edema and only 1 caused deviation of the midline structures. Hydrocephalus was present in 62.5% of patients.

Hydrocephalus

A third endoscopic ventriculostomy was performed in 1 patient and a ventricle-peritoneal shunt and an external ventricular shunt were subsequently placed due to complications; 1 patient was treated with a ventricle-peritoneal shunt and subsequently an external ventricular shunt was placed for ventriculitis during the postoperative period. Of the 5 patients who were treated with ventricle-peritoneal shunts, 2 ended up with an external ventricular shunt due to system exposure or infection; only 1 of the patients was treated with external ventricular bypass onset due to their poor clinical condition.

Treatment

Of the patients described, 50% were tributary to surgery for tumor resection due to their good clinical condition, 25% underwent biopsy and the remaining 25% were unable to undergo surgical treatment for rapid neurological deterioration. In 2 of the operated patients, a resection of 80%, in 1 patient a partial resection and in 1 a total resection was achieved. Of the total number of patients who

underwent surgery, 2 suffered complications secondary to surgery (infection of the surgical site and hypovolemic shock).

Surgical preparation

The hospitalization time until surgery was 6 ± 4.96 days, in 3 cases situations occurred that caused the surgery to be deferred at least once due to medical complications and / or in-hospital management problems.

Histopathology

Histopathological diagnoses of cranial tumors were confirmed in 6 of the 8 patients in the series and 1 was confirmed with a biopsy of a lesion originating in the dorsal spine with great growth in the abdomen and which was carried out by the specialty of Pediatric Surgery. Histopathological diagnoses were: Neuroblastoma in 2 cases, choroid plexus tumor (papilloma and carcinoma) in 2 cases, plexiform neurofibroma in 1 case, retinoblastoma with intracranial extension in 1 case, and ependymoma in 1 case; only 1 patient had no confirmed diagnosis, although the initial clinical suspicion was medulloblastoma. (Table 2)

Complementary treatment

50% of the patients received complementary cancer treatment with chemotherapy, 1 patient received therapy with Gamma Knife ®.

Hospitalization and mortality

The global average hospital stay was 24.12 ± 16.59 days, 50% of the patients died during it, 2 patients did not continue with the post-discharge follow-up and 2 are alive (survival of 4 and 42 months respectively). (Table 2)

DISCUSSION

The incidence of neoplasms of the central nervous system in children is low and its prevalence varies according to the different age groups. [1,3,14,18] It has been described that around 10% of CNS malignancies occur in children under one year of age and up to 25% in children under 3 years of age.[1,2,9,14] In our study, the frequency reaches 5% of the total of neoplasms diagnosed in pediatric patients.

According to sex, there was a slight predominance towards the male sex; the average age of diagnosis was around 12 months, which could be expected according to the age range studied. [14, 18]

The pathological history in this context becomes important due to the relationship with hereditary diseases such as neurofibromatosis (whose early diagnosis could avoid developmental delay) or secondary to harmful factors whose pathophysiology continues to be poorly understood by what is being studied.[5, 13, 16, 17, 18] In the presented series, it was not possible to completely collect information on exposure to chemical substances during pregnancy, so the investigation of these factors should be deepened in future studies which seek to clarify this topic, the same as not It is studied in the context of developing countries.[18]

The most frequent clinical picture was that of irritability and vomiting, at the same time the neurological deficit defined mainly by alteration of the cranial nerves was equally relevant, all of them related to lesions of the posterior fossa, midbrain and signs of intracranial hypertension, which is expected in pediatric patients [5,9,14,18]. Proptosis, visual disturbances and / or ophthalmoparesis with laterality were present in a similar proportion, signs that were more common in supratentorial lesions; the same ones that were the most frequent injuries in our series of patients, as well as in other consulted series of patients younger than 24 months [11, 8].

In publications such as Krivoy A., Cassano J., Bruce C., Conti U., and Villarejo F., endocranial hypertension syndrome is cited as the one with the highest infant presentation, being characterized by macrocephaly, tense fontanel and vomiting. in that order of frequency [6,22,23,24,25]. Based on the above, it can be concluded that in the age group studied the semiology is quite nonspecific.

The diagnostic test of choice was simple skull tomography, added to a contrast-enhanced CT, which provided useful information to determine the characteristics of each of the tumor lesions. In this series of patients, only 50% of the children were able to undergo a brain magnetic resonance (MRI) study, in part determined by the unavailability of the equipment in the medical unit in which they were treated, or due to neurological deterioration. That prevented its realization due to the need for transfer. However, MRI was considered a fundamental requirement for planning the surgical approach to lesions for total resection purposes (50% of cases). In cases where a biopsy was the indication (25%), the surgical intervention was performed regardless of brain MRI studies.

As part of the surgical planning, neurophysiological studies were carried out in order to objectify the brain function, finding alterations in the visual, auditory and lemniscal pathways; Theses studies could not be performed in the postoperative period due to the patient's death or loss to follow-up. The average waiting time between diagnosis and surgical resolution was 6 days, which, at first glance, seems not to be related to the outcome of the patients.

In our series, 2 patients could not be operated on for diagnostic or therapeutic purposes due to the deterioration of their clinical condition and the location of the lesion; Only in one of them was the histopathological diagnosis (neuroblastoma) completed by biopsy of a lesion occupying the abdominal cavity that extended from the dorsal spinal cord. According to the degree of resection, total resection was possible only in 1 of them, 25% benefited from a wide resection and 1 was classified as a partial resection; Surgical conduct as expected is mainly affected by the location of the lesion due to the risks and complications. [2, 4, 12, 13]

The most frequent histopathological diagnoses were Neuroblastoma and Choroid plexus tumors, findings consistent with series reported in pediatric patients of similar age ranges, although it should be mentioned that in no case was the diagnosis of pilocytic astrocytoma, medulloblastoma or ependymoma that would be diagnostic options to consider in this group of patients, thus in the Bruce and Conti series 23 astrocytoma and medulloblastoma are described as the most frequent tumors in children younger than 2 years.

In other series such as that of Hinojosa et al. (in a series of 9 neonates) teratomas, glioblastomas, oligodendrogliomas,

TABLE 2: Characteristics of CNS tumors in pediatric patients operated on at the Baca Ortiz Pediatric Hospital, Quito-Ecuador. 2016-2019

Paholds	Type of injury	Location	Relationship	Location	Histopathology	Sequelae	Mortality
1	Single	Supratentorial	Extra-axial	Intraventricular (third ventricle)	Choroid plexus papilloma	None	No
2	Single	Infratentorial	Intra-axial	Cerebellum	Ependymoma	Aphonia	Yes
3	Single	Supratentorial	Extra-axial	Frontal - extraconal orbital	Retinoblastoma	Blindness	No
4	Single	Supratentorial	Intra-axial	Frontal - orbital	Neurofibroma plexiform	Blindness	No
5	Single	Infratentorial	Intra-axial	Extrusion	No	None	Yes
6	Multiple (abdomen)	Supratentorial	Extra-axial	Zygomatic (extra-cranial)	Metastatic neuroblastoma	None	No
7	Multiple	Supratentorial (Temporal); Infratentorial (cerebellum)	Intra-axial	Protuberance, cerebellum	neuroblastoma	None	Yes
8	Single	Supratentorial	Extra-axial	Intraventricular	Choroid plexus carcinoma	Left Hemiplegia	Yes

Source: Medical records, Baca Ortiz Pediatric Hospital. (Made by Flores C.)

medulloblastoma are described as the most frequent tumors [6]. In Venezuela, authors such as Krivoy A. mention medulloblastoma as the most frequent infratentorial tumor and astrocytoma in the supratentorial region, In this age group 22. Tomita et al., for their part, describe 6 cases of ependymoma in children under the age of 2 years [21].

In our investigation, tumor lesions were determined as intra and extraaxial in a similar proportion (50%), being the most frequent locations the intraventricular, fronto-orbital and protuberance. No predominance of midline tumor lesions was found, expected according to the age group studied. [8]

The frequency of brain tumors in the younger infant group is not clearly understood, largely due to the rare frequency with which neoplasms of the nervous system occur at this age. There are important series of several decades of follow-up such as Siegel's in his cancer statistics, and Lundar in Norway that describes 30 patients aged between 1 and 182 days (6 months), treated with surgery for primary resection. In this last series, 22 patients had supratentorial lesions and 8 were located in the posterior fossa; likewise, 18 corresponded to low-grade tumor lesions (plexus papilloma or astrocytomas) and 12 were high-grade (medulloblastomas / PNET 6, ependymoma 2, glioblastoma 2, teratoma and choroid plexus carcinoma 1 each; gangliogliomas and hamartomas they were reported with 2 cases each [6, 11].

In other series, it was described that the infratentorial and supratentorial PNETs were the most frequent, followed by ependymomas and brainstem gliomas; Atypical teratoid-rhabdoid tumors and choroid plexus carcinomas are also less frequently described below 2 years of age. [11, 12].

The high incidence of plexus tumors among CNS malignancies during the first year of life is known, therefore that their frequency should not be underestimated 8. Considering the frequency with which primary CNS tumors are diagnosed in the age group studied in this series, the results presented can be used as a model to establish clinical characteristics of the pathology's debut.

Treatment with adjuvant chemotherapy was performed in 37.5% of patients according to histopathological diagnosis after considering the side effects that contraindicate radiotherapy treatment in this age group [2, 3, 9, 10, 20], the same that should be considered only in cases where resection of the lesion is not possible, due to its toxicity, clearly described.

Mortality during hospitalization (in cases treated and not treated with surgery) was 50% and was associated with great neurological deterioration in the postoperative period, so it was not considered a tributary to new surgical intervention. Likewise, 25% of the patients did not continue with the outpatient follow-up, so their outcome is unknown and 25% (N = 2) were alive during the last evaluation, presenting a survival of 4 and 42 months (Papilloma of choroid plexus and neuroblastoma respectively). The small size of this study group and the follow-up time have limited the description of definitive survival and mortality, although series with up to 70% 5-year survival are described, results that are encouraging and dependent on the quality of the study surgical resection also [3, 13].

It is known that brain tumors diagnosed before one year of life are considered to have a poor prognosis. This prognosis is related to the congenital incidence of the pathology, the tumor size (large) and the aggressiveness of high-grade tumors that have a poor response to antineoplastic therapy[7,8,9]. In the series consulted, such as that of Lundar, important survival rates during the follow-up are described since stable results were obtained from 20 survivors in the long term, [18] of them with good quality of life, according to the authors - Barthel of 100 in 18 of 20 patients [6]. At As stated at the beginning of this introduction, the main

prognostic factor was the quality of the surgical resection, followed by the location of the neoplasm and its histological type. [6, 13]

In relation to low-grade gliomas, it is known that the age of less than 2 years at the time of diagnosis was recognized as a risk factor for mortality [12, 18]. Series such as those by Lundar and Isaacs describe an increase in mortality in patients who underwent early radiotherapy treatment [6,9]; Although radiotherapy can increase survival, its limitation is the greater possibility of generating sequelae. It is also mentioned that children of an early age have a better tolerance and recovery of the immediate postsurgical neurological deficit over time, as reported in the previously cited series [6,9].

Neoplastic CNS lesions have a rapid and fulminant course with high associated mortality, known and previously described in the follow-up series [2, 8, 9]. Investigating the presence of malignant cells in cytology is considered important (specificity close to 95%) of cerebrospinal fluid due to its correlation with neoplasia, determination of disease progression, requirement of different modalities of radiation treatment and prognosis. [1, 20]

Among the limitations of this study, it should be considered that, due to the small number of patients, the percentages may not correctly reflect an epidemiological reality, so these findings in no way rule out the distribution by topography and histopathological diagnosis described in series of patients. more extensive [1, 5, 6, 11].

CONCLUSION

CNS tumors in children between 0 and 2 years of age are not frequent, their location is predominantly supratentorial and their vital prognosis is uncertain, although it essentially depends on their histological type.

Treatment with radiotherapy in this age group is an option to consider only in cases without the possibility of surgical resection due to comorbidities and associated sequelae, so surgery for resection purposes constitutes the basis of treatment in these patients.

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