Original Article

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Posterior Fossa Tumors in Infants: 13-year single center retrospective review.

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Introduction/Background: Central nervous system (CNS) tumors in infants are rare, ranging between 1 and 10% of all pediatric CNS tumors. The infratentorial location is a challenge to neuro-oncologist and -surgeons due their subtle clinical presentation, different histopathological types, biological behaviors, and anesthetic-surgery difficulties.
Methods: Single center retrospective study of infants diagnosed with posterior fossa tumors between 2010 and 2023.
Results: Nineteen patients were included. Mean age 8.8 months; eight males. The most common presenting symptom was torticollis (n-6, 31.6%), followed by vomiting (n-3, 15.8%) and increased head circumference (n-3, 15.8%). Atypical Teratoid Rhabdoid Tumor (AT/RT) was the most common subtype (n-11, 57.9%), followed by Medulloblastoma (MB). Metastatic disease at diagnosis was evident in five cases. Seventeen patients initially underwent correction of hydrocephalus. Regarding surgical resection, one (5.3%) patient underwent biopsy, 13 (68.4%) complete resection, four (21%) partial resection. Only one patient, diagnosed with ependymoma, did not receive chemotherapy after surgery, 14/19 received high-dose chemotherapy, eight of these followed by autologous bone marrow transplantation (ABMT). Focal radiotherapy (RT) was performed in four patients with AT/RT and in one ependymoma, following ABMT and complete resection, respectively. Event-free survival at 2 and 5 years was 64.9% and overall survival 63.2% and 54.2% respectively.
Conclusion: Despite aggressive histological subtypes, neurosurgical challenges, and limitation of adjuvant therapy, we have shown acceptable survival rates in this challenging group of patients showing the importance of appropriate supportive care, improvement in surgical techniques and a multi-professional approach.

Keywords: pediatric posterior fossa tumors, infratentorial tumors,infant tumors, embryonal tumors

INTRODUCTION

Central nervous system (CNS) tumors in infants, defined as brain tumors occurring in children less than one year of age, are rare and variable in the literature, ranging between 1 and 10% of all pediatric CNS tumors (1-3). The infratentorial location is very rare in this age group (1,4) and is a challenge to pediatric neuro-oncologist and neuro-surgeons due their subtle clinical presentation, different histopathological types, biological behaviors, and anesthetic-surgery difficulties (1,4).

This 13-year retrospective review aims to analyses the characteristics of infant posterior fossa tumors treated at a tertiary center in an upper-middle-income-country.

MATERIALS AND METHODS

Single center retrospective study of infants diagnosed with posterior fossa tumors at Pediatric Oncology Institute (IOP-GRAACC)/ Federal University of Sao Paulo, between 2010 and 2023.

Demographic and clinical-pathology characteristics (presenting symptoms, tumor pathology, surgical management, treatment modalities and outcomes) were recorded. Histopathological samples were analyzed by a pediatric pathologist specialist at our institution.

Categorical variables were described as number and percentage. Continuous nonparametric variables were reported as median (range). Event-free survival (EFS) was defined as the time from diagnosis to the progression. Overall survival (OS) was defined from the diagnosis until death for any cause or last assessment. Kaplan–Meier method was used to estimate survival curves for

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progression-free survival and overall survival. The software SPSS-IBM 29 was used for all analyses. Ethics approval was obtained at study center prior to study commencement.

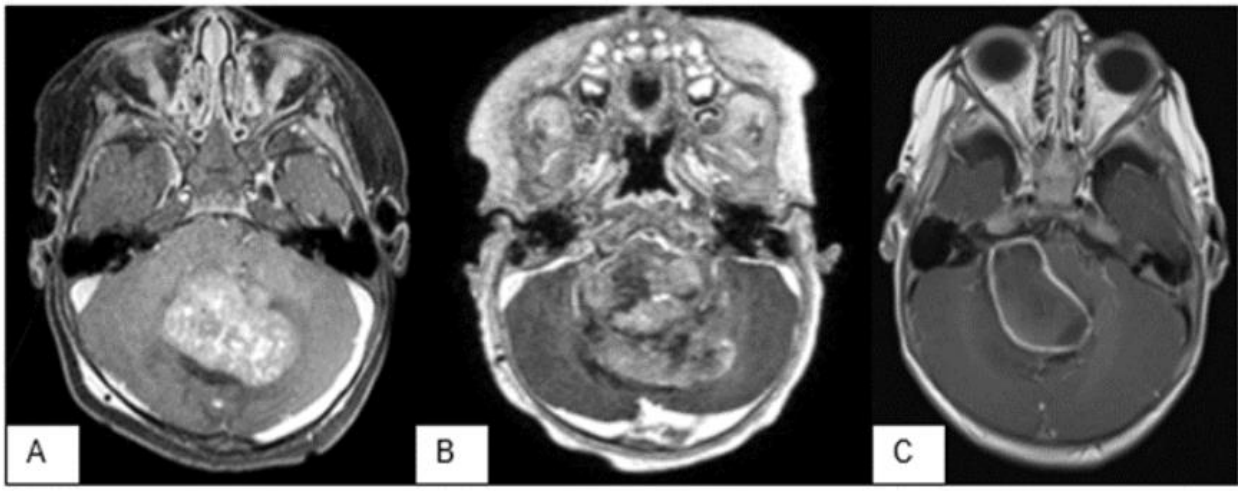

Figure 1 - Posterior fossa tumors A: Medulloblastoma; B: Atypical Teratoid Rhabdoid Tumor; C: Ependymoma

RESULTS

Patients' characteristics and tumor subtypes

Nineteen patients with posterior fossa tumors less than one year-old were included. Median age was 8.8 months (range,4-12m); eight (42.1%) were male. The most common presenting symptom was torticollis (n-6, 31.6%), followed by vomiting (n-3, 15.8%) and increased head circumference (n-3, 15.8%). Less frequent signs and symptoms were hypotonia and regression of developmental milestones (n-2, 10.5%), drowsiness (n-2, 10.5%), irritability (n-2, 10.5%) and squint (n-1, 5.3%).

Atypical Teratoid Rhabdoid Tumor (AT/RT) was the most common subtype (n-11, 57.9%), followed by Medulloblastoma (MB) (n-5, 26.3%), Ependymoma (n-2, 10.5%) and Immature Teratoma (n-1, 5.3%). Metastatic disease as classified by Chang et al (5) at diagnosis was evident in three MB patients (2 M2, 1 M1) and in two AT/RT cases (1 M1, 1 M3). Figure 1 shows magnetic resonance images of three cases.

AT/RT cases were diagnosed based on loss of INI-1 expression on immunohistochemistry (IHQ); MB classified into possible molecular subgroups (MB-WNT, MB-SHH and MB non-SHH/non-WNT) using magnetic resonance image radiogenomics and IHQ markers (b-catenin, GAB, YAP) with three patients with desmoplastic nodular histology and GAB and YAP positive classified as MB sonic hedgehog (SHH). For ependymomas, histone loss in immunohistochemistry was used to classify into possible Group A (PFA).

Treatment modalities and outcomes

Surgical procedures were performed by a team of pediatric onco-neurosurgeons. Seventeen patients initially underwent treatment of hydrocephalus through third ventriculostomy (n-1, 5.3%) or placement of a ventriculoperitoneal shunt (n-16, 84.2%). Regarding surgical resection, one (5.3%) patient underwent biopsy, 13 (68.4%) complete resection, four (21%) partial resection, two of which were followed by second-look surgery. Nine patients experienced peri- or postoperative complication as follows: cranial nerve deficits (n-3), ventriculitis (n-2), surgical wound dehiscence (n-1), CSF leak over the wound (n-1), tumor bed bleeding (n-1), subdural hematoma (n-1), ventriculoperitoneal shunt dysfunction (n-1). Mortality rate due to surgical complications was zero.

Only one patient, diagnosed with ependymoma, did not receive chemotherapy after surgery, 14/19 received high-dose chemotherapy according to Head Start (6) backbone scheme, eight of these followed by autologous bone marrow transplant (ABMT), five patients with AT/RT died due to progressive disease during induction chemotherapy. Three patients with desmoplastic-nodular MB, classified as SHH, were treated with conventional chemotherapy, one of then recurred one-year later with leptomeningeal cerebellar disease was treated with high dose chemotherapy and ABMT and unfortunately died due septic shock during the treatment. Focal radiotherapy (RT) was performed in four patients with AT/RT as part of the initial treatment following ABMT and in one ependymoma following complete resection. Three patients with ATRT received craniospinal RT at recurrence and one ependymoma as palliative care.

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Treatment modalities are described in table 1.

With a median follow-up of 22 months (range, 3-123), event-free survival at 2 and 5 years was 64.9% and overall survival 63.2% and 54.2% respectively, for the entire cohort (Figures 2 and 3). According to histology, 5/11 AT/RT, 1/2 ependymomas, 4/5 MB and the patient with immature teratoma are alive without disease.

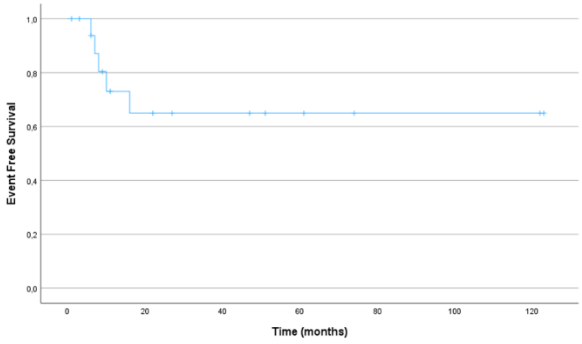

Figure 2 - Event Free Survival

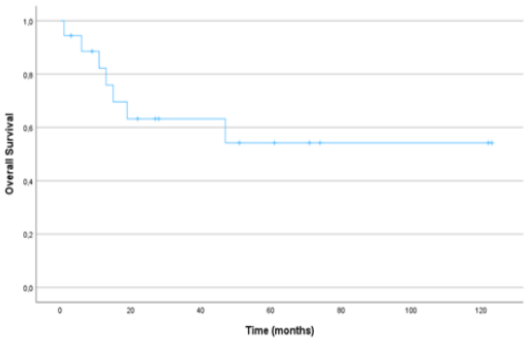

Figure 3 - Overall Survival

Table 1- Treatment modalities

	Chemo	High-dose Chemo	ABMT	RT
AT/RT	-	11	6	5
Medulloblastoma	3	2	-	-
Ependymoma	1	-	-	2
Immature Teratoma	-	1	-	-

ABMT: autologous bone marrow transplantation; AT/RT: Atypical teratoid rhabdoid tumor; Chemo: chemotherapy; RT: radiotherapy

DISCUSSION

In view of the rarity and challenges of this group of patients our review analysed the characteristics of nineteen patients during a 13-year period. In the study period, 106 patients were diagnosed with CNS tumors under one year of age, 17.9% in the posterior fossa, similarly than report in the literature (1,3,4).

Clinical presentation can be very subtle in this age group (1,2). Signs and symptoms related to increased intracranial pressure can be delayed due to the fontanelles that allow for the stretching of the head. In our cohort in addition to the most commons signs described we reported six cases with torticollis (31.5%), a higher incidence than reported in the series of Picariello et al (4).

Due to increased intracranial pressure as presentation, cerebrospinal fluid (CSF) diversion is almost always required before tumor resection. There is no consensus on the best management of hydrocephalus (1,4,7). In our scenario whereas most of the cases are treated first at an emergency department and then referred to a specialized center is expected that most common procedure was the VP-shunt. Only one patient experienced shunt disfunction as surgical complication.

Considering the histology and location, complete resection is one of the main points of treatment (2,4,8) and very challenging due to the increased risk of complications related to anesthesia and tumor location in this group of age (1,8). Some of the complications described due to location are cerebellar syndromes, cranial nerve deficits, hydrocephalus and CSF leaks (8) but literature on perioperative complication rates in pediatric neurosurgery is scarce (8-10). In our series we described some complications with no mortality related to surgical procedures.

In the neonatal period, teratoma is the most common brain tumor, comprising almost 50% of the cases (1,11), although in the first year of life the predominant histology belongs to embryonal tumors, specially AT/RT that is the most common brain tumor in children younger than one-year (12), and MB that accounts for 50% newly diagnosed brain tumors in children less than two years of age (1) what is in agreement with our report.

Challenges regarding surgical procedures and aggressive behavior imply on very poor overall survival rates in this group of children (2,3). Aiming to delay radiotherapy due to unacceptable consequences as developmental deficits and endocrinologic disturbances, most recent trials explored strategies as high-dose chemotherapy with ABMT, intraventricular chemotherapy and focal radiation (13). For MB, these more intensive approaches have resulted in better survival, and the molecular understanding is refining the prognostic characteristics for each subgroup (13,14), however, for CNS embryonal tumors other than MB the outcome remains unsatisfactory (13) and as described in our

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cohort 6/11 (54.5%) of the patients with AT/RT died due to progressive disease, five during induction chemotherapy. The prognostic implications of molecular sub-groups ATRT-TYR, -SHH and -MYC are still under evaluation (12). For the ependymomas, despite the small number of patients in our cohort, due to the image characteristics and unfavorable outcome, associated with histone loss in immunohistochemistry, it suggests that they belong to subgroup A, which generally demonstrates worse survival with surgery and focal radiotherapy as standard of care (12).

The limitations of our study are the retrospective design and the absence of a multi-professional analyses to report functional outcomes of this selected cohort of patients.

CONCLUSION

In conclusion, despite aggressive histological subtypes, neurosurgical challenges, and limitation of adjuvant therapy, we have shown acceptable survival rates in this challenging group of patients showing the importance of appropriate supportive care, improvement in surgical techniques and a multi-professional approach.

ACKNOWLEDGMENTS

DISCLOSURES

Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the local Ethics Committee "Comitê de Ética em Pesquisa Universidade Federal de São Paulo"

Consent to participate

The patients gave consent to use their information and images for research purposes. *Consent for publication*

The patient gave consent to use his information and images for publication.

Conflict of interest

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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CONTRIBUTIONS

-**Natália Dassi**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing

-**Carolina Silva de Aguiar**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft

-**Patricia A Dastoli**: Conceptualization, Formal Analysis, Investigation, Methodology, Writing – original draft

-Nasjla S Silva: Conceptualization, Formal Analysis, Investigation, Methodology, Writing – original draft

-Sergio Cavalheiro: Conceptualization, Investigation, Methodology, Validation

-Andrea M Cappellano: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editingConceptualization, Investigation, Methodology, Validation

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