

BRAIN TUMORS IN THE FIRST THREE YEARS OF LIFE

A review of twenty cases

Adriana Ávila de Espíndola¹, Hamilton Matushita¹, Juliana Martins Pimenta², Ana Cristina da Silva Fernandes², Sérgio Rosemberg³, Umbertina Conti Reed¹

ABSTRACT - Objective and Method: To review the clinical and neuropathological findings as well as the type of therapy and outcome in 20 infants under 3 years-old with central nervous system (CNS) tumor. They were treated at the Department of Neurology, "Hospital das Clínicas" University of São Paulo Medical School, from January 1997 to May 2001. **Results:** Astrocytoma was the most common histological type (n=7), followed by ependymoma (n=3), medulloblastoma (n=2), craniopharyngioma (n=2) and desmoplastic ganglioglioma (n=2). The location of the tumor was predominantly supratentorial. Mean follow-up time was 20.2 months with recurrence in 7 cases. For each type of tumor we have emphasized the treatment currently recommended. **Conclusion:** Although follow-up time is not sufficient for analyzing survival, a trend of improvement in prognosis was noted, compared to another series of cases from our Institution that had been evaluated before 1990.

KEY WORDS: brain tumors, children, central nervous system tumors, neuro-oncology treatment.

Tumores do sistema nervoso central nos primeiros três anos de vida: revisão de vinte casos

RESUMO - Objetivo e Método: Avaliar os aspectos clínicos e histopatológicos, o tipo de tratamento e a evolução de 20 crianças menores de três anos de idade, com o diagnóstico de tumor de sistema nervoso central, que foram tratadas em nossa Instituição no período de janeiro de 1997 a maio de 2001. **Resultados:** O astrocitoma foi o tumor mais comum (n=7), seguido pelo ependimoma (n=3), medulloblastoma (n=2), craniofaringioma (n=2) e ganglioglioma desmoplásico infantil (n=2). A localização do tumor foi predominantemente supratentorial. A média de seguimento foi 20,2 meses e houve recidiva em sete casos. Para cada tipo de tumor enfatizamos o tipo de tratamento recomendado na atualidade. **Conclusão:** Embora o tempo de seguimento não seja suficiente, ainda, para analisar a sobrevida, foi notada nítida tendência a melhor prognóstico em comparação com a casuística proveniente de nossa Instituição que analisou casos abordados antes da década de 90.

PALAVRAS-CHAVE: tumores cerebrais, crianças, tumores do sistema nervoso central, tratamento neurooncológico.

Nearly 8 to 20% of central nervous system (CNS) tumors occur in children under three years of age¹. The prognosis is usually poor² due to difficulties in surgical technique, the malignant histology most of these tumors and the impossibility of treating with radiotherapy^{3,4}. The rate of survival is low, around 20 to 40%^{4,5}; however, after 1980, some institutions have obtained better rates of prognosis, reporting 56% of survival at 5 years and normal neurological development after treatment in 50% of the patients⁶⁻⁸. In small infants the most common histological types are ependymoma, medulloblastoma, choroid plexus papilloma, astrocytoma and teratoma. Supratentorial tu-

mors are almost twice as frequent, particularly in the first year of life^{9,10}.

Clinical signs and symptoms are usually not specific, therefore causing diagnostic delay. The most common clinical manifestations depend on increased intracranial pressure, vomiting, macrocephaly, drowsiness/lethargy and delay in neurological development^{9,11}. Focal neurological changes are more commonly observed in the second year of life¹⁰.

We report the histopathological, clinical, therapeutic and progressive aspects of twenty patients under three years of age during the period from January 1997 to May 2001.

¹Neurology Department, University of São Paulo Medical School, São Paulo SP, Brazil (FMUSP); ²Medical Student, FMUSP; ³Pathology Department, FMUSP.

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Dra. Adriana Ávila de Espíndola - Avenida Dr. Enéas de Carvalho Aguiar 255 / 5º andar / sala 5031 - 05403-000 São Paulo SP - Brasil. E-mail: adrianaespindola@uol.com.br

METHOD

From January 1997 to May 2001, 20 children under three years of age at diagnosis among 84 with CNS tumor were treated in the Department of Neurology, "Hospital das Clínicas", University of São Paulo Medical School (FMUSP).

The diagnosis in all patients was established by magnetic resonance imaging (MRI). The following items were analyzed: patient's age and sex, topography and histology of the tumors, clinical features until the diagnosis, results achieved by surgeries, surgical complications, adjuvant therapies, management of recurrences, and follow-up of the patients.

Tables 1 and 2 exhibit these variables

This study was approved by the Ethics Committee for research projects of our Institution protocol number 015/99.

RESULTS

Patients' ages ranged from 6 months to 35 months and the group included 13 boys and 7 girls. In 15 cases

(75%) the tumor was supratentorial, in 4 (20%) it was infratentorial and in one (5%) it was spinal.

The most common histological type was astrocytic in 7 cases, followed by ependymoma in three cases and two of each of the following: medulloblastoma, craniopharyngioma and desmoplastic infantile ganglioglioma. The other tumors were neurofibroma, choroid plexus carcinoma, choroid plexus papilloma and atypical teratoid/rhabdoid tumor, one case of each. The astrocytic tumors were classified as: 3 pilocytic astrocytomas, 2 low grade astrocytomas, one subependymal giant cell astrocytoma in a patient with tuberous sclerosis and one mixed oligoastrocytoma.

The length of clinical complaints before diagnosis varied from one day to 17 months (mean 4.36 months).

The first clinical manifestations were: epileptic sei-

Table 1. Central nervous system tumors: location, histological diagnosis and clinical features in 20 children under 3 years of age.

Case	Sex	Age	Location	Histological diagnosis	Clinical features	Length of time before diagnosis
1	F	2y	Cerebellum	Pilocytic astrocytoma	Increased intracranial pressure	3 days
2	M	1y9m	Optic pathways	Pilocytic astrocytoma	Motor deficit	15 days
3	M	7m	Optic pathways	Pilocytic astrocytoma	Proptosis; visual loss	7m
4	M	1y	Subependymal	Giant cell astrocytoma	Asymptomatic (West syndrome)	5m
5	M	1y6m	Brainstem	Low grade glioma	Motor deficit	8m
6	F	2y9m	Left parietal lobe	Low grade glioma	Epileptic seizures	2m
7	M	2y5m	Left parietal lobe	Oligoastrocytoma	Epileptic seizures	1y5m
8	M	1y	Cerebellum	Medulloblastoma	Motor deficit	1m
9	F	2y8m	Cerebellum	Medulloblastoma	Increased intracranial pressure; ataxia	15 days
10	F	1y6m	Sellar/suprasellar	Craniopharyngioma	Visual loss	11m
11	M	2y11m	Sellar/suprasellar	Craniopharyngioma	Epileptic seizures; visual impairment	5m
12	M	1y7m	Left parietal lobe	Ependymoma	Motor deficit	3 days
13	M	1y4m	IV ventricle	Ependymoma	Ataxia	4m
14	M	1y3m	Right hemisphere	Anaplastic ependymoma	Motor deficit	2m
15	F	1y	Left temporal lobe	Desmoplastic infantile ganglioglioma	Epileptic seizures	9m
16	M	6m	Left temporal lobe	Desmoplastic infantile ganglioglioma	Epileptic seizures	2m
17	M	2y	Left parieto-occipital lobe	Choroid plexus carcinoma	Increased intracranial pressure	1 day
18	F	1y1m	Left parieto-occipital lobe	Choroid plexus papilloma	Epileptic seizures	5m
19	F	2y6m	Right hemisphere	Atypical teratoid/rhabdoid tumor	Motor deficit	2m
20	M	8m	Extradural L1-L5	Neurofibroma	Motor deficit	6m

y, years; m, months.

Table 2. Central nervous system tumors: type of treatment and follow-up in 20 children under 3 years of age.

Case	Tumor location and histological diagnosis	Type of surgical resection	Chemotherapy	Radiotherapy	Recurrence	Treatment of recurrence	Follow-up
1	Cerebellar astrocytoma	Total	No	No	No		Disease-free; normal neurological outcome
2	Optic pathways astrocytoma	Partial	Yes	Yes	Yes	Resection + radiotherapy	Residual disease; delayed neurodevelopment + motor deficit
3	Optic pathways astrocytoma	Partial	No	No	No		Died
4	Subependymal astrocytoma	Total	No	No	No		Disease-free; normal neurological outcome
5	Brainstem astrocytoma	Only biopsy	Yes	Yes	No		Residual disease; motor deficit
6	Hemispheric astrocytoma	Total	No	No	No		Disease-free; normal neurological outcome; seizures
7	Hemispheric oligoastrocytoma	Total	No	No	No		Disease-free; normal neurological outcome
8	Medulloblastoma	Subtotal	Yes	No	No		Residual disease; cerebellar mutism
9	Medulloblastoma	Total	Yes	Yes	No		Disease-free; motor deficit
10	Craniopharyngioma	Total	No	No	No		Disease-free; visual loss
11	Craniopharyngioma	Bleomycin catheter	Yes	No	Yes	Waiting new resection	Residual disease; normal neurological outcome
12	Hemispheric ependymoma	Total	Yes	No	Yes	Resection + chemotherapy	Disease-free; normal neurological outcome
13	IV ventricle ependymoma	Total	No	No	Yes	Resection	Died
14	Hemispheric anaplastic ependymoma	Total	No	No	Yes	Resection + radiotherapy	Residual disease; normal neurological outcome
15	Desmoplastic infantile ganglioglioma	Total	No	No	No		Disease-free; normal neurological outcome
16	Desmoplastic infantile ganglioglioma	Partial	No	No	Yes	Resection	Residual disease; normal neurological outcome
17	Choroid plexus carcinoma	Total	N	Yes	Yes	Resection	Residual disease; new recurrence; normal neurological outcome
18	Choroid plexus papilloma	Total	No	No	No		Disease-free; normal neurological outcome
19	Atypical teratoid/rhabdoid	Total	Yes	No	No		Disease-free; normal neurological outcome; abandoned follow-up
20	Neurofibroma	Total	No	No	No		Disease-free; motor deficit; abandoned follow-up

zures in 7 patients, motor deficit in 7, severe visual deficit in three, increased intracranial pressure in two and ataxia in two patients. The diagnosis in the patient with tuberous sclerosis was made during investigation for West syndrome.

All patients underwent surgery for tumor removal. Total excision was achieved in 14 patients (70%) and a subtotal removal (at least 90%) in one patient with medulloblastoma (5%). Partial removal, (i.e. from 50 to 90%), was obtained in three patients (15%), two of them with optic pathways astrocytoma and one with desmoplastic infantile ganglioglioma. Biopsy, corresponding to less than 50% of tumor resection was performed in one patient with low grade brainstem

astrocytoma (5%) and in one patient with craniopharyngioma (5%) a catheter was employed for bleomycin infusion.

Surgical complications occurred in 5 patients (25%): two patients with medulloblastoma had cerebellar mutism; one patient with craniopharyngioma manifested panhypopituitarism; one patient with ependymoma developed meningitis, and one patient with desmoplastic infantile ganglioglioma had hemiparesis.

Adjuvant chemotherapy was administered to 4 patients, one patient was treated with radiotherapy and three patients with both chemotherapy and radiotherapy. The patients treated with chemotherapy

suffered from medulloblastoma (case 8), craniopharyngioma (case 11), ependymoma (case 12) and atypical teratoid/rhabdoid tumor (case 19). The patient with choroid plexus carcinoma (case 18) was treated with radiotherapy, and the patients treated with both, chemotherapy and radiotherapy had optic pathways astrocytoma (case 2), brainstem glioma (case 5) and medulloblastoma (case 9).

Follow-up ranged from one month to 3 years and 8 months, mean of 20.2 months.

Tumor recurrence at follow-up was present in 7 patients whose tumor type was: optic pathways pilocytic astrocytoma (case 2), craniopharyngioma (case 11), ependymoma (cases 12, 13 and 14), desmoplastic infantile ganglioglioma (case 16) and choroid plexus carcinoma (case 17).

The patient with optic pathways glioma underwent a new surgery and radiotherapy; at follow-up residual disease was encountered and delay in neurological development (already noticed prior to diagnosis). The patient with craniopharyngioma had a normal neurological outcome; the cyst disappeared after bleomycin therapy but during follow-up the solid part of the tumor has grown and the patient is currently awaiting a surgical procedure. All three patients with ependymoma (cases 12, 13 and 14) underwent a new surgery. Case 12 was also treated with chemotherapy and at the moment of this report he has no apparent disease and shows normal neurological development. Case 13 died due to a late surgical complication (respiratory distress). Case 14 received radiotherapy, and is developing normally although with residual tumor.

The patient with desmoplastic infantile ganglioglioma (case 16) was submitted to a new attempt of tumor resection but removal was partial once again. However, he no longer has epileptic seizures and shows normal neurological development.

The tumor in the patient with choroid plexus carcinoma (case 17) was totally removed again but despite chemotherapy a new recurrence was detected by neuroimaging at the last examination.

Two patients were lost to follow-up: case 19 had atypical teratoid/rhabdoid tumour and after receiving chemotherapy, went back to his home town to start radiotherapy and was lost to follow-up; case 20, with spinal neurofibroma located between L1-L5 also abandoned the follow-up.

DISCUSSION

In a previous study on brain tumors, which involved 460 children aged 0 to 15 years treated at our

Institution from 1962 to 1989¹², 40 children (8.7%), were less than two years of age. That study indicated a slight predominance of infratentorial tumors (IT), particularly of medulloblastoma followed by ependymoma. Among the supratentorial tumors (ST), choroid plexus tumors, astrocytoma and primitive neuroectodermal tumors constituted the three most frequent tumors. In the present study, we observed a change in the epidemiological distribution of the tumors, in patients under age two. ST was more predominant than IT and the histological distribution was more varied: two cases of ependymoma, choroid plexus tumor, infantile desmoplastic ganglioglioma and optoquiasmatic pilocytic astrocytoma, one case of craniopharyngioma and one case of subependymal giant cell astrocytoma in a boy with tuberous sclerosis.

We believe that the advances in neurodiagnostic imaging, particularly of MRI, permitted more precise and earlier diagnosis of some low density parenchymal tumors, most of them detected during epileptic seizures (7/20 patients had epileptic seizures), and more facilities of our citizens in getting healthcare, contributed to the changes in tumor distributions. An additional observation was the higher incidence (23.8%) of CNS tumors among children younger than three in the present study, compared to that found in the literature, which reports a range from 8 to 20%¹³. Very few institutions in our country are referral centers for pediatric neurosurgery and neurology, particularly when medical care for infants is necessary. Related to a greater incidence of ST in this population study group, it seems there is also a trend in the literature¹³.

Age influences some of the clinical features of these very young patients. It is a well known fact that due to cranial and cerebral plasticity of young children and the difficulty they have in referring symptoms, the intracranial tumor may grow silently without producing significant neurological changes^{14,15}. In our study histology and topographic distributions were the main factors determining the length of symptoms. Excluding case 20, a spinal tumor, we found 14 benign and 5 malignant tumors. Additionally, five cases (cases 3, 5, 7, 10, 15) had over 6 months of clinical symptoms, two of them were hemispheric tumors causing epilepsy (cases 7 and 15), and one each of brain stem astrocytoma, optic pathway astrocytoma, and craniopharyngioma. This resulted in 5 out of 14 benign tumors against 0 out of 5 malignant tumors with length of symptoms of more than 6 months.

Regarding topographic distribution, midline tumors were present in 7/19 patients and lateralized tumors in 12/19 patients. Three patients out of 7 (42.8%) with midline tumors and 2 patients out of 12 (16.6%) with lateralized tumors had symptoms for longer than 6 months. Symptoms related to increased intracranial pressure (ICP) were present in only three children; patients with posterior fossa tumor in two, and choroid plexus tumor in one case. It has been agreed to be a cause of increased ICP, through obstruction of CSF leading to hydrocephalus. Mechanisms of increased ICP in patients with choroid plexus tumors, has been controversial. Tumor size and disturbance of CSF production or obstruction are the most acceptable mechanisms¹⁶.

Other signs and symptoms exhibited in our patients were closely related to the functional anatomy of the site where the tumors originated. For example: case 3 with optochiasmatic glioma had nystagmus and proptosis observed in the neonatal period.

Brain tumors may be found, incidentally and very early in the patient's life, as in children harboring some neurocutaneous diseases. This was the situation with case 4, who presented with a tumor in the lateral ventricle, in the neighborhood of the foramen of Monro, during investigation of an epileptic syndrome (West syndrome), as a part of tuberous sclerosis.

The most important goal in the treatment of brain tumors in infants is the complete surgical resection of the lesion. The malignant histological nature of the tumor at this age may also affect the prognosis but not as significantly as the extension of tumor resection⁹. In a recent study with 39 children younger than three years of age, the extension of tumor removal was the most important prognostic factor¹⁰. The only

exception was the optic pathways gliomas¹⁷. Adjuvant chemotherapy can be indicated depending on the histological diagnosis and the amount of the surgical removal. In the last 20 years chemotherapy has become a meaningful resource in the therapeutic plan for a brain mass in young children in whom irradiation can cause cognitive and endocrine side effects³. Chemotherapy may postpone radiotherapy until the child is older or may even defer radiotherapy³.

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