INTERDISCIPLINARY APPROACH IN BRAIN TUMORS IN CHILDREN - RETROSPECTIVE STUDY IN CLINIC III PEDIATRICS

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Abstract

Brain tumors in children are the most common solid tumors in pediatrics, occupying the second place among neoplasia after acute lymphoblastic leukemia. In the past 20 years, the mortality of brain tumors (0.8 out of 100,000) exceeded the mortality due to acute lymphoblastic leukemia (0.4 out of 100 000) (1). This shows that tumor management with intracranial location is a challenge to the medical world and requires an interdisciplinary approach with the participation of pediatrician, neurosurgeon and radiotherapist. Our study wanted to be a retrospective analysis of 28 cases of brain tumors selected from the oncological pathology of Pediatric Clinics III of Children's Emergency Hospital, diagnosed and treated for a period of 10 years, seeking an interdisciplinary approach to improve quality of life and an increase in the survival rate of these children.

Keywords: brain tumor, child, interdisciplinary approach

Introduction

Brain tumors are neoplasms of central nervous system (CNS) cells, representing the second largest group (2). It is a heterogeneous group of diseases characterized by high histological variability, but their common elements are the intracranial location and difficulty of treatment due to this critical location. Data from the Surveillance, Epidemiology and Final Outcomes (SEFO) program from 1973 to 1989 showed an incidence of 2.8 cases per 100 000 children per year and a mortality rate of 45%. Epidemiological data suggest an increase in the incidence of brain tumors in children although they are not very clear and some specialists disagree with this. It is supposed to be a false increase in the incidence of intracranial tumors following the development of diagnostic imaging techniques. (1) They are associated with significant morbidity due to motor and intellectual deficits due to both the tumor itself and the treatment. Two incidence peaks were described: the first in children up to 10 years with an incidence of 2.5 cases per 100 000 children a year with a slightly male predominance (1.1: 1) and the second in decades three and four. Etiology for most tumors with CNS localization is unknown at present, but known risk factors are ionizing radiation, immunosuppression and association with genetic syndromes. (1, 2, 3) A study conducted in 2013 showed that there is a significant risk of developing a brain tumor after conventional radiation therapy. (4) Exogenous immunosuppression occurs in transplant patients and is associated with an increase in the incidence of SNL localized lymphomas. (5) Endogenous immunosuppression in patients with Wiscott-Aldrich syndrome or ataxia-telangiectasia is associated with an increased frequency of primary CNS lymphomas. (1,2,3). Genetic syndromes such as type I neurofibromatosis (NFI), type II Neurofibromatosis (NF II), Gorlin, Gardner, Li-Fraumeni, Turcot, von Hippel-Lindau syndrome, Tuberous sclerosis and type I endocrine neoplasia are most often associated with brain tumors .(3)

The classification of tumors with intracranial localization has been in continuous dynamics in recent decades due to advances in diagnosis and improvement of knowledge. It is important to have a more accurate fit for the correct treatment. The most commonly used is the World Health Organization (WHO) classification based on the histological appearance of the tumors, which is also the most important element in the choice of treatment. (8)

In terms of location, brain tumors may be: supratentorial localized in or in contact with the cerebral hemispheres, more common in adults; infratentorial located in the posterior cerebral fossa, in the cerebellum, in the cerebral trunk or in contact with these, more common in children and basal tumors that originate in the structures of the skull base (bone, meninges, nerve structures) or are invaded by tumor formations of the structures adjacent (rhino pharyngeal, mucous bone sinuses, vascular structures). (3)

The main objectives of the paper were to evaluate the need for an interdisciplinary approach from the moment of diagnosis by analyzing the clinical and par clinically aspects that allowed the framing and staging of diseases, on the one hand, and the choice of therapy and the pursuit of survival and evolution until the end of life, on the other.

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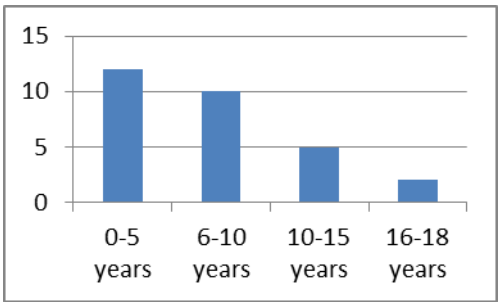

Fig.1. Distribution by age group

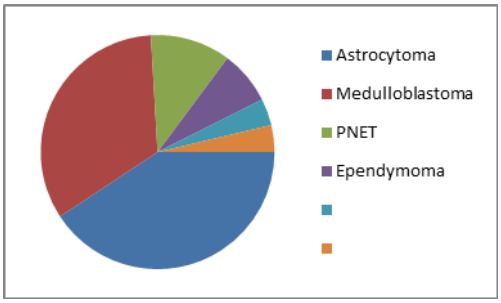

Fig.2 Distribution by histological type

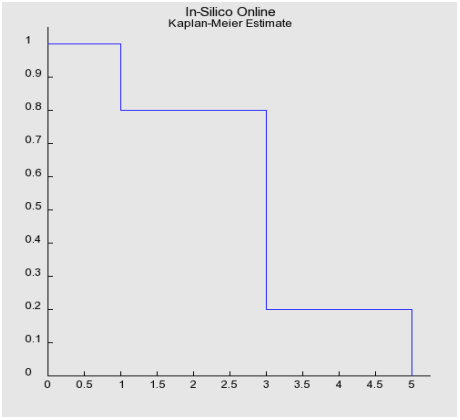

Fig. 3. Kaplan-Meier curve for general survival analysis

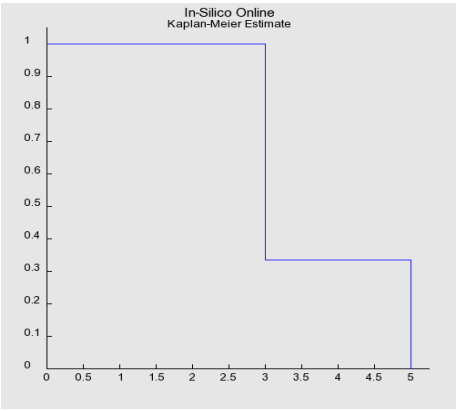

Fig. 4. Kaplan Meier Survival Curve for Astrocytoma

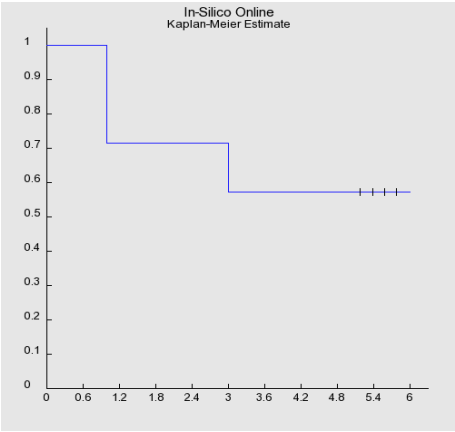

Figure 5. Kaplan-Meier survival curve for Medulloblastoma

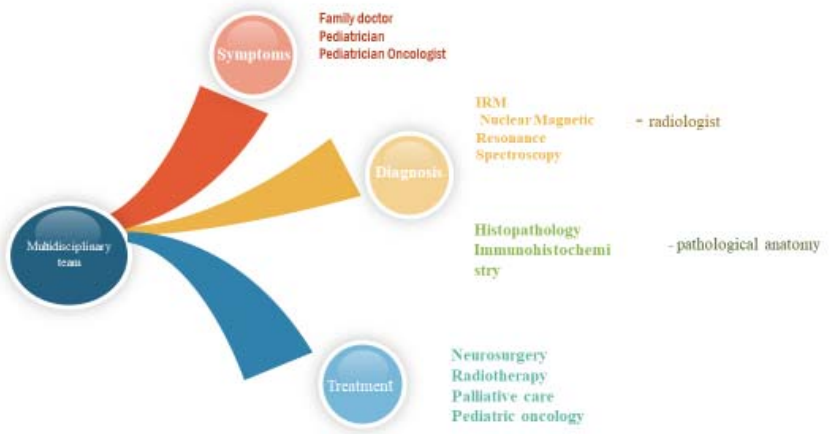

Fig. 6. The interdisciplinary approach

	Number of deaths	Number of survivors	Total
Subtotal ablation	5	6	11
Total ablation	2	14	16
Total	7	20	27

Table 1. Survival contingency chart at 3 years depending on the type of surgery

	Number of deaths	Number of survivors	Total
Subtotal ablation	6	5	11
Total ablation	4	12	16
Total	10	17	27

Table 2. Contingency Table of Survival at 5 Years Depending on Type of Surgery.

Material and method

The study group was comprised of 28 cases of children diagnosed with intracranial tumor selected from the total cases of pediatric neoplastic pathology admitted and treated on the Department of Pediatric Oncology of the Emergency Clinical Emergency Hospital for Children Louis Turcanu Timisoara during 2006-2016. Patients are aged between 1 and 17 years old with a ratio of boys: girls 1.33: 1. The criteria for inclusion in the study were: age under 18 years, tumor diagnosis with intracranial location, oncology treatment: surgical resection, chemotherapy and / or radiotherapy, possibility to follow up the patient for 5 years after diagnosis except for those deceased at less than 5 years after diagnosis. For each patient, we looked at the following issues: age, gender, background (rural or urban); histological type and tumor location (infratentorial or supratentorial), symptoms present at diagnosis; (total or subtotal) surgical ablation, radiotherapy or chemotherapy as well as evolution and survival The data obtained from the observation sheets (with the opinion of the ethics committee of the institute) were statistically analyzed by EpiInfo and the Kaplan-Meiner survival curves were calculated.

Results and discussions

Analyzing the gender distribution in the 28 patients study group, 16 are male and 12 female represented 57%, respectively, 43%. The boys / girls ratio is 1.33 to 1. As far as the environment of origin is concerned, 11 patients are urban and 17 rural, representing 39%, respectively, 61%. The median of the diagnostic age is 6 years old and the average diagnosis age is 6.9 years old. Most patients were diagnosed between 0-5 years (12 cases) and as we approach the age of 18, the number of diagnosed cases decreases progressively. In the age range of 16-18 years, only 2 cases were recorded (Fig. 1). Data from literature shows the highest incidence of SNC tumors to be in children aged 12 months to 6 years. (6)

Taking into account histological types of CNS neoplasm: Astrocytoma was the most commonly diagnosed tumor, accounting for 39% of the total of 28 cases, followed by Medulloblastoma by 32%. There were 3 cases of PNET (10%), 2 cases of Ependymoma (7.14%), 1 Glioblastoma and 1 case of Oligodendroglioma (Fig. 2). Our data are comparable to those in literature, pilocytic Astrocytoma being the most commonly diagnosed intracranial tumor in the pediatric population in the US. (6) In terms of location: 64% of the tumors have infratentorial localization and 36% supratentorial. These data overlap with those in literature, the most common localization described in pediatric patients being infratentorial. (3)

In 67% of the patients the most common symptom in diagnosis was headache, followed by nausea and vomiting 53%. In 75% of patients, there were signs and symptoms of intracranial hypertension, in 46% cognition and balance disorders were present, in 32% brain nerve damage, epileptic seizures in 32% and in 17% hemiplegia / hemiparesis. According to an outpatient study, in 75 patients aged 5 months to 16 years, the most common symptoms in diagnosis were headache (51% of cases), vomiting (51% of cases), seizures (24%), and personality changes (11% of cases). New imaging techniques are MRI and Positron emission CT (CT) and with agents such as fluorodeoxyglucose (FDG) that have a high sensitivity (92%) and specificity (69%) in the differentiation of radiation-induced necrosis tumor recurrence compared to conventional MRI and are required in current practice. (9, 10)

The first step in the treatment of tumors with intracranial location is surgery. Exceptions to this therapeutic strategy are infiltrative diffuse Glioma and globular chiasmatic Glioma in patients with Neurofibromatosis type 1 (NF1) because tumor resection does not influence prognosis and diagnosis can only be determined by MRI.

The purpose of surgery is total resection (if possible), being the main prognostic factor for Ependymoma, small grade Glyoma, Craniopharyngioma, Meduloblastoma, high grade Glioma. Nevertheless, aggressive resection increases the risk of short and long-term morbidity and mortality. (3)

Out of the 28 patients enrolled in the study, in 27 (96%) surgery was recommended and performed. The only case in which neurosurgical intervention was not performed was a case diagnosed at a very advanced stage in which surgery was not possible and would not have brought any additional benefit to progression and prognosis. Out of the 27 neurosurgical patients treated, in 11 (40%) there was subtotal ablation and the remaining 60% benefited from total macroscopic ablation. Total ablation is also the major prognostic factor for these patients. The limitations of surgical intervention related to localization and technique make prognosis in brain tumors to be unfavorable.

Overall systemic chemotherapy was performed according to the histological type in 82% of the patients, some of whom also had local chemotherapy administered via an Ommaya reservoir (25% of all patients). Most of the patients (46%) received maximum treatment consisting of surgical ablation with chemotherapy and radiotherapy. The second place as a therapeutic strategy is the combination of surgical ablation with chemotherapy performed in 32% of patients. Radiotherapy can be used for curative or palliative purposes. There are differences in the sensitivity of tumors to radiotherapy, for example Medulloblastomas are more sensitive than Glioblastomas, and the indication of radiotherapy is made considering histology results. (7)

Radiotherapy was performed in 57% of patients in combination with chemotherapy and / or surgical ablation. Alternatives to fractionated radiotherapy could be performing hyper-fractured radiotherapy that allows a higher total dose to be given in a larger number of smaller adverse reaction radiation sessions. Out of the 28 patients, only one performed hyper-directed radiotherapy outside of our country. Patients' access to hyper-fractionation radiotherapy should be considered, as this type of therapy could bring additional benefits in terms of both quality of life and progression and prognosis. (6)

The main complications of chemotherapy (22 patients who underwent chemotherapy) were: bacterial infections (95%), aplasia (90%), candidiasis (59%), toxic hepatitis (50%) and bleeding (31%). 13 patients (46%) were admitted to the department of anesthesia and intensive care. 92% of the patients survived 1 year, 3% lost to 71% and 5% survived only 53% of the patients. And of those who survived, of those who survived over 5 years there were 4 more deaths, which means that the survival rate has fallen to 39%.

Neurological tumors generally fall into high or low grade strata and generally higher grade tumors have poorer survival, however, patients with either high grade or low grade tumors suffer the adverse effects of chemotherapy, radiation, surgery, and direct disease sequelae, which may be ameliorated with palliative care. (12)

Of the total patients who underwent subtotal ablation (7), 6 survived at 3 years while the total of those who benefited from total ablation, 14 survived at 3 years (Table 1).

The death risk in patients who have undergone total ablation is 2/16 = 12.5% compared to the risk of death in patients who have undergone subtotal ablation that is 5/11 = 45.4%. The relative risk is 3.6, which means that the group of patients undergoing subtotal ablation has a 3.6-fold higher risk of death at 3 years than the group of patients

who have undergone total ablation. The same type of contingency table was used to calculate the risk of death at 5 years depending on the type of therapy performed: total ablation, subtotal ablation (Table 2).

The results show that the risk of death at 5 years for those who performed subtotal ablation is 54.5%, whereas in patients where total ablation was possible it is 25% with a 29% risk difference p = 0.07 with a confidence interval of 95.5%. These results shows that the values obtained have no statistical significance, probably due to the small number of cases included in the study.

For the survival analysis we used the Kaplan-Meier survival curve. The figure below is the time axis, meaning the years of survival from diagnosis (1, 3 and 5), and the percentage of deceased patients at 1.3 and 5 years, starting from a 100% survival, that is, the value 1 on the graphic.

Figure 3 shows that approximately 20% of patients died from the total of deaths in the study at one year. Three years after diagnosis, the highest death rate (approximately 60%) was recorded and 20% of all deaths were diagnosed 5 years after diagnosis. These results could be an alarm signal for the period in which we have the greatest risk of losing a patient with intracranial tumor.

Figure 4 shows the Kaplan Meier survival curve for Astrocytoma at 1, 3 and 5 years. Of all deaths by astrocytoma, no death is recorded at 1 year after diagnosis. Three years after diagnosis the highest death rate is recorded (over 60%), and at the age of 5 from the time of diagnosis, approximately 40% of all deaths by Astrocytoma are recorded.

Figure 5 shows the Kaplan Meier survival curve for Medulloblastoma. Unlike Astrocytoma, in the case of Medulloblastoma, deaths are also recorded one year after diagnosis (about 30% of the total) and at 3 years 20% of all Medulloblastoma patients die. The interdisciplinary approach in our study, from diagnosis to treatment, is illustrated in figure 6.

Palliative care was imposed at diagnosis to a case that was surgical unapproachable, in two cases that died in the first months of treatment and in all cases with unfavorable progression to death. Survivors of neoplasia with intracranial location had an increased rate of neurological squeal secondary to treatment including strokes, motor impairment, hearing loss, increased risk of stroke or the occurrence of Meningioma or other secondary therapies for chemotherapy and radiotherapy.(3)

A palliative consult for patients with brain tumors is associated with longer survival and better quality of life. In the ENABLE III study, patients who received early palliative oncology care had significantly longer 1 year survival rates than who received delayed palliative care. (11)

Conclusions

In our study, the most affected age group was 0-5 years totaling a number of 12 patients diagnosed with CNS tumors, followed by the age range of 6-10 years in which 10 patients were diagnosed. The histological type of CNS tumor most commonly diagnosed was Astrocytoma followed by Meduloblastoma and PNET. Surgical treatment was used in 27 of 28 patients with or without chemotherapy and radiotherapy. One of the prognostic factors identified in the study is the type of ablation (total or subtotal), subtotal ablation patients with a 3-year-risk death rate, 3.6 times higher than those who benefited from total macroscopic ablation. The limits of surgical intervention are related to localization and technique. Radiotherapy was performed in 57% of the patients in combination with surgery or chemotherapy. It has become necessary for the interdisciplinary approach to be formed by pediatrician, neurosurgeon, radiotherapist, intensive care physician and palliative care specialist.

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