INTRACRANIAL EPENDYMOMAS IN CHILDREN

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Abstract: Ependymomas are malignant glial tumors of the central nervous system. Although they are recognized in all age groups, they are more frequent in children, accounting for between 5 and 10% of all pediatric intracranial tumors. Due to its aggressive nature and fairly frequent occurrence in the pediatric population, our study was conducted to specify the epidemiological, clinical, and paraclinical profile as well as to evaluate the therapeutic means and results and the follow-up in 24 children collected in the neurosurgery department, CHU IBN ROCHD over 12 years (from January 2012 to December 2023). The age of our patients ranged from 1.5 to 17 years, with a mean age of 8.29 years, of which 10 were girls and 14 were boys. Headaches associated with nausea and vomiting were the most frequent symptoms. Time to consultation ranged from 1 to 7 months, with an average of 4 months. Radiologically, an MRI was performed on all patients with infratentorial localization (FCP). The most frequent histological type was WHO grade III ependymoma. Surgery, and more specifically, complete excision, is the cornerstone of ependymoma treatment. In our series, 13 children underwent adjuvant external radiotherapy, with a 14-week mean time between surgery and radiotherapy. 54.16% of the children in our series received chemotherapy. In terms of evolution, we have 50% of our patients alive, 56.33% in complete remission after 3 years, 16.66% deceased, and 25% lost to follow-up. Childhood ependymoma is a pathology in the throes of change. The new anatomomolecular classification opens up unprecedented prospects for a detailed understanding of therapeutic strategy. The mainstay of treatment is complete surgery, and the role of radiotherapy remains essential in children.

Keywords: ependymomas, pediatric, posterior fossa, malignant tumors, radiotherapy.

EPENDYMOMES INTRACRÂNIENS CHEZ LES ENFANTS

Résumé : Les épendymomes sont des tumeurs gliales malignes du système nerveux central. Bien qu'ils soient reconnus dans tous les groupes d'âge, ils sont plus fréquents chez les enfants et représentent entre 5 et 10 % de toutes les tumeurs intracrâniennes pédiatriques. Du fait de son caractère agressif et assez fréquent chez la population pédiatrique, notre étude a été menée afin de préciser le profil épidémiologique, clinique et paraclinique ainsi que d'évaluer les moyens et résultats thérapeutiques et le suivi chez 24 enfants colligés dans le service de neurochirurgie, du CHU IBN ROCHD sur une période de 12 ans (du janvier 2012 au décembre 2023). L'âge de nos malades était compris entre 1.5 ans et 17 ans, avec un âge moyen de 8.29 ans, dont 10 sont des filles et 14 sont des garçons. Les céphalées associées aux nausées et aux vomissements étaient les symptômes les plus fréquents. Le délai de consultation variait de 1 mois à 7 mois avec une moyenne de 4 mois. Radiologiquement, une IRM a été réalisée chez tous nos malades ayant objectivé des localisations infratentorielles (FCP). Le type histologique le plus fréquent était l'épendymome de grade III de l'OMS. La chirurgie et plus spécifiquement, l'exérèse complète, est la pierre angulaire du traitement des épendymomes. Dans notre série, 13 enfants ont bénéficié d'une radiothérapie adjuvante externe avec un délai moyen entre la chirurgie et la radiothérapie de 14 semaines. La chimiothérapie a concerné 54.16 % des enfants de notre série. Sur le plan évolutif, 50 % de nos malades sont en vie, dont 56.33 % sont en rémission complète après 3 ans, 16.66 % sont décédés, et 25 % sont perdus de vue. L'épendymome de l'enfant est une pathologie en plein bouleversement. La nouvelle classification anatomomoléculaire ouvre des perspectives inédites sur la compréhension fine de la stratégie thérapeutique. La base du traitement repose sur une chirurgie complète et le rôle de la radiothérapie reste essentiel chez l'enfant.

Mots clés : épendymomes, pédiatrique, fosse cérébrale postérieure, tumeurs malignes, radiothérapie.

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Introduction

Ependymomas are neuroepithelial tumors derived from a neoplastic transformation of the ependymal cells that line the ventricular system. They belong to the group of glial tumors, which are uncommon in children. They account for 6.5% of central nervous system tumors [1] and 1.6% of all pediatric cancers [2].

90% of these tumors are intracranial, and almost two-thirds of them are found in the Posterior Cerebral Fossa (PCF). These tumors develop from the ependymal cells lining the cerebral ventricles and the central canal of the spinal cord, or filum terminale [3]. The World Health Organization (WHO) 2021 anatomopathological classification distinguishes ependymomas according to supratentorial or PCF location, based also on molecular biology, which, more recently, has confirmed these differences [3]. A number of factors influence the prognosis of pediatric intracranial ependymomas. These include the quality of surgical resection, postoperative radiotherapy, age at diagnosis, histological grade, and tumor location. All these factors play a crucial role in assessing the prognosis of this pathology in children. Despite advances in neuroimaging, neurosurgery, and postoperative adjuvant therapy, the prognosis of pediatric ependymomas is still relatively poor compared with that of other childhood brain tumors.

Our work aimed to report on the neurosurgery department's experience at the CHU IBN ROCHD ANNABA, present a review of the literature on the epidemiological, clinical, paraclinical, and therapeutic features of this type of tumor, and assess patient follow-up and overall survival.

Materials and methods

A retrospective study of 24 cases of intracranial ependymoma in children managed in the neurosurgery department of CHU IBN ROCHD ANNABA (ALGERIA) during 12 years, spread between January 2012 and December 2023. We included all patients aged between 0 and 17 years, including those admitted to our department during the study period, with histological confirmation and an exploitable record. Diagnostic features were radiological, intraoperative, and histological.

Cerebral Computed Tomography (CT) was performed in 5 mm-thick axial slices in all patients without and with contrast injection, and cerebral MRI was performed with a 1.5 Tesla machine in T1—and T2-weighted sequences in all patients in all three planes of space without and with gadolinium injection. A cerebral CT was used for postoperative monitoring. Statistical analyses were meticulously performed using SPSS software. These analyses correspond to a description of our data series by calculating means and medians for quantitative variables and numbers, frequencies, and percentages. Regarding ethical considerations, data collection was carried out for patient anonymity and confidentiality.

Results

The mean age of our patients was 8.29 years, with extremes ranging from 1.5 to 17 years, with male predominance (14 boys vs. 10 girls) (a sex ratio of 1.4). Headaches associated with nausea and vomiting were the most frequent symptoms. Time to consultation ranged from 1 to 7 months, with an average of 4 months. Radiologically, all our patients undergo a CT scan.

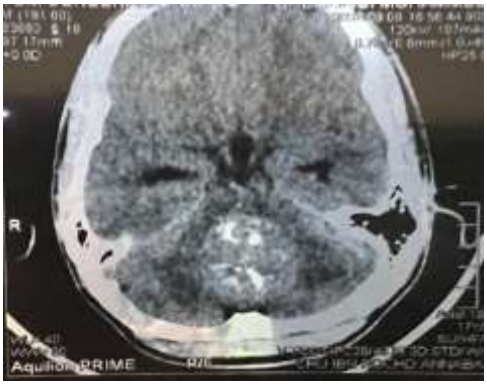

Figure 1. Cerebral CT scan of a PCF ependymoma shows intratumoral calcifications.

MRI scans were performed in all our patients, and all sites were found to be intracranial infratentorial (FCP), with no metastatic extension to the lumbar region.

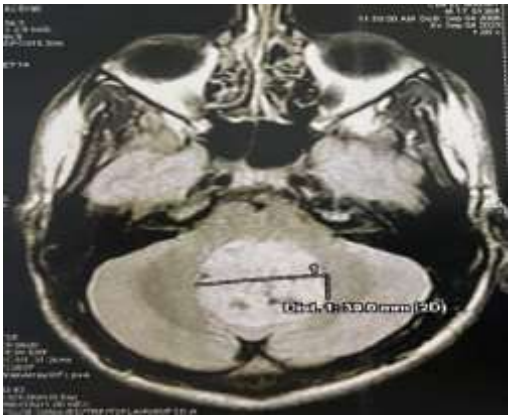

Figure 2. Brain MRI shows an ependymoma filling V4.

The most frequent histological type was WHO grade III ependymoma, accounting for 13 cases or 54.16%.

Table 1. Different anatomopathological types of ependymoma

Anatomopathological types	Effective	Percentage %
Subependymomas and myxopapillary ependymomas	0	0
Classic ependymomas	11	45.83
Anaplastic ependymomas	13	54.16
Total	24	100

Surgery, and more specifically, complete excision, is the cornerstone of ependymoma treatment. All patients in our series underwent excision, 47% of which was subtotal. In our series, all children aged over 5 years (13 children) benefited from external adjuvant radiotherapy, with an average delay between surgery and radiotherapy of 14 weeks. Chemotherapy was used in 54.16% of the children in our series.

In terms of evolution, 50% of our patients are still alive, of whom 56.33% are in complete remission after 3 years, 16.66% have died, and 25% have been lost to follow-up.

Discussion

Estimating the incidence of ependymoma is complex; in France, the annual rate is 2.6 per million

children (2.4 for brain tumors and 0.2 for spinal cord tumors, respectively). This represents 6.5% of all central nervous system tumors [1], [5].

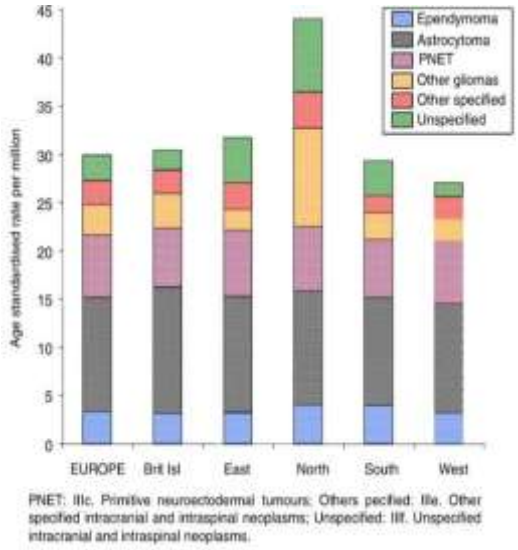

Figure 3. Incidence of central nervous system (CNS) tumors in children (0–14 years) in Europe, 1988–1997 by diagnostic group and region (n =11,829).

Age-standardized rates (ASR), world standard population [6]. East: Belarus, Estonia, Hungary, Slovakia; British Isles: England, Scotland, Northern Ireland, Ireland, Wales; North: Denmark, Finland, Iceland, Norway; West: Germany, France (regional pediatric registries and general registries), Netherlands, Switzerland; South: Spain, Italy, Malta, Slovenia, Turkey [7].

According to the literature, ependymoma is most common in children under 5 years of age. McGuire et al. reported a mean age of 5 years for infratentorial forms, 7.8 years for supratentorial forms, and an overall mean age of 6.6 years (0-18 years) [8].

Our patients' ages at diagnosis ranged from 1.5 years (minimum age) to 17 years (maximum age). The mean age was 8.29 years. These results are similar to those reported in the literature.

The occurrence of ependymomas is higher in boys than in girls, as confirmed by several studies, including a French study of 251 cases, of which 144 were boys and 107 were girls [5]. Studies carried out in India [9], Australia [10], Italy [11], and Turkey [12] have also corroborated these findings, highlighting a consistent male predominance. Our study is in line with the literature. In a study carried out in the UK [13], it was found that the time taken to diagnose symptoms was less than 6 months for 80% of patients, i.e., 34 cases out of 43. The most frequent times for diagnosis were between 1 and 2 months and between 3 and 4 months. In 77% of supratentorial cases and 80% of infratentorial cases, the time to diagnosis was less than 6 months. Clinical symptoms are non-specific and vary according to tumor location, size, and malignancy. Intracranial hypertension syndrome is the main mode of presentation in our study. It usually manifests as a headache accompanied by vomiting. This is in line with the study by VAIDYA K. et al., 29% (67 cases) of headache versus 28% (65 cases) of vomiting [10].

Improved imaging techniques have made it easier to diagnose intracranial expansive processes and guide surgical procedures. These techniques have several advantages:

Firstly, it is part of the positive diagnosis, then part of the tumor extension assessment, and finally, part of the impact assessment and therapeutic follow-up. Swarzt et al. [14] found that the majority of intracranial ependymal tumors developed in the posterior fossa (19/26 cases), representing 73% of the series studied. This result is in agreement with the findings of our study, in which all our patients who underwent CT scans showed a lesion localization in the posterior cerebral fossa. The most common location of ependymal tumors in the PCF is intraventricular [15]. According to Svien et al. [16], PCF tumors develop in the margins of the fourth ventricle. This observation was validated by research carried out by Swarzt et al. [14]. According to Naidish et al. [17], supratentorial ependymal tumors also tend to develop in the intraparenchymal region (85%). The study by Swarzt et al. [14] also supports this, with 83% intraparenchymal localizations. Supratentorial ependymomas tend to be larger than their infratentorial counterparts. The series of studies by Armington et al. [18] showed a 94% frequency of tumors larger than 4 cm, whereas most infratentorial ependymomas were significantly smaller [14], [17]. Cystic formations are typical of supratentorial ependymomas. According to Swarzt et al. [14], the cystic component was observed in 84% of supratentorial cases (4/6 cases), while 95% of infratentorial cases (14/15 cases) lacked the cystic component. All our patients presented solid masses without associated cystic formations, which is consistent with the literature. Around 50% of supratentorial and infratentorial ependymomas present with dense, punctate calcification. Armington et al. [18] found calcifications in six of the tumors, representing 38% of cases. Magnetic resonance imaging (MRI) is the main imaging modality used for the evaluation of intracranial and spinal ependymoma.

According to the literature, classical and anaplastic ependymomas are the most common histopathological subtypes in children.

According to Desandes et al. [5], classical cases account for 51%, followed by anaplastic ependymomas at 39% and myxopapillary ependymomas at 7.6%. In our study, the most frequent ependymal tumors were anaplastic ependymomas (grade III) (54.16%), followed by classic ependymomas (type II) (45.83%). Anaplastic forms were more frequent before the age of five. Classical ependymoma was the most frequent histological type from the age of 10. Our results are similar to those of Desandes et al. In our patients, anaplastic forms were present in patients aged between 3 and 6 years. Classical forms were present in 58% of patients under 10 years of age and in 42% of patients over 10 years of age.

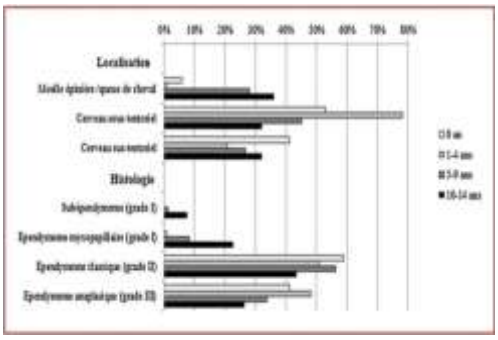

Figure 4 - Distribution by age group of ependymal tumors by location and histological type in children aged 0 to 14 years (National Registry of Solid Tumors in Children, France, 2000-2008) [5].

Dissemination at the time of ependymoma diagnosis is generally rare. In the vast majority of patients, primary tumors in the posterior fossa indicated that posterior fossa ependymomas may be more important for dissemination than supratentorial ependymomas. Any patient with suspected ependymoma, particularly in the posterior cerebral fossa, should benefit from craniospinal MRI, if possible, preoperatively [19]. In our series, no spinal dissemination was observed.

Current therapeutic management of pediatric ependymomas is based on extensive surgical excision, complemented by adjuvant therapy. In most cases, this treatment combines radiotherapy with or without chemotherapy. If the tumor cannot be safely resected due to its location, a biopsy of the lesion is always necessary. When tumor resection is feasible, the most extensive resection is always desirable. Numerous clinical studies have shown that extensive resection is associated with both progression-free survival and overall survival [16], [20]. Surgical resection is more difficult in infratentorial cases due to the frequent involvement of the brainstem and several cranial nerves [21]. Higher rates of complete resection for supratentorial ependymomas probably explain the better prognosis and disease-free survival rates of children with tumors [22].

In the series by Van et al. [23], mortality was 7.2% (6 patients) due to intraoperative complications dominated by air embolism, tumor bleeding, and cardiovascular instability. In our series of studies, we did not record any cases of intra- or postoperative mortality.

Radiotherapy is currently considered a standard adjuvant treatment after resection of intracranial ependymoma [24], [25], with a significant difference in survival for patients receiving radiotherapy at a dose greater than 45 Gy [26].

A strategy of adjuvant chemotherapy after surgery and radiotherapy in children with newly diagnosed intracranial ependymoma over 3 years of age was initially tested by Needle et al. [27]. 19 children aged 3 to 14 years received systemic therapy with carboplatin, vincristine, ifosfamide, and etoposide. The 5-year survival rate was 74%, which is superior to most contemporary series reported and suggests that adjuvant chemotherapy may play a role in improving tumor-related outcomes. In our series, of the 13 patients treated with chemotherapy, 11 children received postoperative chemotherapy

in consideration of their young age of less than 3 years, to avoid irradiation.

Massimino et al. prescribe brain MRI with gadolinium for intracranial ependymomas every 3 months for approximately 1-2 years, then 4 months and 6 months at 5 years. Beyond 5 years, recommendations for MRI vary [28].

Approximately 25–50% of children experience relapse despite current treatment protocols, which include surgery and adjuvant radiotherapy [29]. The tumor usually recurs locally at the site of the primary tumor [30]. Ependymomas don't usually have leptomeningeal metastases, which is when the tumor spreads through the pericerebral subarachnoid spaces to the ventricles, spinal cord, or lumbosacral nerve roots. In our study series, 41% of patients had a local recurrence at the same primary site.

Overall, the 10-year vital prognosis is 65% [31] and depends on several factors: the quality of surgical resection is significantly correlated with survival in the most recent series in the literature [32]. In patients with completely resected tumors, 5-year survival is estimated at between 67% and 80%. Among patients with incompletely resected tumors, 5-year survival estimates range from 22% to 47% [33]. In our series, of the 8 patients still alive, 7 underwent subtotal resection, which explains their survival. Of the patients who died as a result of tumor progression, and two initially underwent incomplete surgical resection. They survived 1.8 years after initial surgical treatment.

Age at diagnosis can also be an important prognostic factor. Outcomes in very young children are generally poorer [33]. For children under 3 years of age at diagnosis, Pollack et al. [34] reported a 5-year survival estimate of 22%. In older children, the estimated 5-year survival is 75%. In our series, 54.54% (6 children) of children under 3 years of age died, and survival between initial treatment, which is surgery, and death was 18 and 21 months.

Historical studies have shown that ependymoma patients receiving radiotherapy had a better outcome than those not treated with irradiation [35], [36].

One of the most controversial prognostic factors in pediatric ependymoma is the histological grade of the tumor. Many reports suggest that patients with differentiated ependymoma have a better outcome than those with anaplastic ependymoma [37].

Conclusion

Ependymomas are the third most common tumor of the pediatric central nervous system, accounting for 6–12% of pediatric brain tumors. The management of these tumors has undergone major changes over the last twenty years, leading to a significant evolution in outcomes. Nevertheless, despite advances in neurosurgery, neuroimaging, and postoperative adjuvant therapy, the management of these tumors remains complex, and a fallout occurs in over 50% of cases, especially in the absence of total

resection prior to conformal radiotherapy. Despite advances in the diagnosis and understanding of the causes of ependymoma, the efficacy of chemotherapy remains uncertain. The development of new therapeutic approaches represents a major challenge for this pathology, which generally requires surgery and radiotherapy and can lead to physical and cognitive sequelae, particularly in young children.

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