

INFRATENTORIAL EPENDYMOMAS IN CHILDREN

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Objective - The aim of the study was to analyse the clinico-pathological characteristics, treatment, complications and outcome in paediatric patients with infratentorial ependymomas.

Patients and Methods - A retrospective analysis of 6 patients younger than 15 years and hospitalized for surgical treatment of infratentorial ependymomas was performed. The intracranial hypertension, neurological status, radiological CT or MRI findings, tumours localization, type of resection, hydrocephalus treatment, histopathology, complications and outcome were analysed.

Results - There were 6 (12%) of children with infratentorial ependymomas among the posterior cranial fossa tumours. The average age of the patients was 48±55 months. The average size of ependymomas was 42 mm. The most common neurological signs and symptoms before diagnostic procedures were high intracranial pressure and ataxia.

Conclusion - The best treatment option for infratentorial ependymomas is surgery with a complete resection whenever possible, followed by radiotherapy and/or chemotherapy taking into consideration the age of the patients and histological characteristics of the tumours.

Key words: Paediatric brain tumours ▪ Ependymoma ▪ Anaplastic ependymoma

Introduction

Posterior cranial fossa tumours account for more than 50% of brain tumours in children (1, 2). In infants there is a significant predominance of supratentorial tumours. The most common location of these tumours is the cerebellar

hemisphere (35-45%), then the vermis (15-20%), the fourth ventricle (15-20%) and the brain stem (13-18%). The most common histological types of these tumours are: astrocytomas, medulloblastomas and ependymomas. Ependymomas account for 9 to 13% of brain tumours in children (3) and 1.2% to 7.8% of all brain tumours (4). They develop from ependymal cells. They most frequently occur in children younger than 4 years (5-7). More than 90% of ependymomas in children develop within the cranium, about two thirds are infratentorial and one third supratentorial. The incidence of the illness in terms of the hemispheres is equal, but for supratentorial ependymomas there is a clear predominance of boys in a ratio of 1.4:1 (8, 9). At the time of diagnosis they most often show their area of insertion on the ventricle wall and often infiltrate into the surrounding tissue.

In view of the fact that ependymomas develop from ependymal cells or their remains, they should always be in contact with the surface of the ventricle, but this is not a rule. Ependymomas may develop in the cerebral parenchyma, in the front of the filum terminale or subarachnoidal spinal space, without connection to the ependym. Macroscopically, they most frequently present as grey or red, lobular or soft tumours, relatively clearly differentiated from other tissue. They are less vascularized than medulloblastomas or rhabdoid-teratoid tumours. They may sometimes have a papillary appearance and point to the papillary plexus.

Microscopically, the degree of cellularity is very varied, even in the same tumour (10). The cells are typically polygonal, arranged around the blood vessels, creating a perivascular pseudo-rosette and sometime true ependymal rosettes. The cells contain microcalcificates which may even resemble metaplastic bone or cartilage (11). There may be cells which produce melanin (12) and signet ring cells (13). Inside the tumour it is possi-

ble to see zones of necrosis and haemorrhage. The microscopic picture with anaplastic ependymomas shows a histological picture of malignancy, with nuclear pleomorphism, hyperchromatism, excessive mitoses, necrosis and disorganized cytoarchitecture.

According to the World Health Organization, ependymomas are defined in 3 grades: grade 1 (sub-ependymomas and myxopapillary ependymomas), grade 2 (cellular, papillary, light cells) and grade 3 (anaplastic ependymomas). The pathohistological difference between ependymomas (grade 2) and anaplastic ependymomas is founded on the presence of nuclear atypia, mitotic activity and hypercellular presence in anaplastic ependymomas. Anaplastic ependymomas have significantly worse prognosis (14). Although supratentorial ependymomas, infratentorial ependymomas and those in the spinal space have a very similar pathohistological picture, they, however, show their own specific genetic abnormalities (15). Ependymoblastomas are extremely malignant embryonic tumours which occur in children in the first two years of life and belong to the group of primitive neuroectodermal tumours (PNET). The intraventricular locations of these tumours enable them to disseminate through the cerebrospinal fluid (CSF) and create distant metastasis.

The clinical picture is dominated by symptoms and signs caused by increased intracranial pressure resulting from the spatial compressive effect of the tumour or hydrocephalus. Symptoms may include headache, nausea, vomiting, irritability, ataxia, visual disturbances and lesions of a peripheral nerves depending on the location, size and speed of growth of the tumour (16).

The treatment of ependymomas requires the maximum possible surgical resection, alongside the use of radiotherapy and/or chemotherapy. Complete surgical resection of the ependymoma often is not possible in

view of its insertion at the base of the fourth ventricle of the brain. Attempts at resection of this part of the tumour may be accompanied by significant post-operative morbidity, especially dysfunction of the upper group of cranial nerves. Radiotherapy is used, as adjuvant therapy, as standard radiotherapy for ependymomas, or as radiosurgery, whilst the use of chemotherapy is limited to children under 3 years and patients with anaplastic ependymomas.

The aim of this study was to analyse the clinico-pathological characteristics, the frequency of symptoms or signs of intracranial hypertension, neurological findings, radiological findings on the initial and follow-up CT or NMR, the localization of the tumour, the scope of resection, treatment of hydrocephalus, and complications and outcome of treatment in paediatric patients with infratentorial ependymomas.

Patients and Methods

The study consisted of a retrospective analysis of patients younger than 15 who were hospitalized for surgical treatment of tumours in the posterior cranial fossa in the Neurosurgical Centre of Hopital Purpan in Toulouse, France, from 13 January 1992 to 28 December 2001. The study included patients who had complete medical documentation consisting of: initial clinical findings, initial CT or NMR of the neurocranium, surgical findings and one or more post-surgical clinical and CT or NMR findings. In this period, 78 patients underwent surgery for tumours in the posterior cranial fossa of which 28 were excluded from the study (17 due to incomplete medical documentation, and 11 patients completed their treatment in other centres). Of the remaining patients who were the subject of the analysis of this study, ependymoma were diagnosed in 6 by pathohistology.

The presence of intracranial hypertension was diagnosed on the basis of clinical findings (headache, vomiting, papillary oedema), dilatation of the ventricular system and loss of subarachnoid space on CT or NMR imaging of the neurocranium. The degree of ventricular dilatation on the CT or NMR was shown by the fronto-occipital horn ratio (FOR) (17). The age of the patients is shown in months. The size of the tumour is expressed in millimetres.

The scope of tumour resection was analysed on the basis of follow-up CT or NMR, 24 hours after surgery. Total resection indicates the surgeon's belief that he did not leave any tumour fragments in the operational field and the absence of any area showing contrast medium on post-surgical CT or NMR. Subtotal resection indicates the presence of a minimal residue after post-surgical CT or NMR. Partial resection assumes the presence of clear areas marked by contrast medium. Patients were followed up by post-surgical NMR every six months. The outcome of treatment was monitored from the admission of the patients to the neurosurgical centre until the latest news on the patient.

Statistical analysis

Statistical analysis was performed using the statistical package by MedCalc software (version 8.1.0.0 for Windows, MedCalc). The results are presented in absolute and relative numbers with the use of mean values and standard deviation.

Results

Of the total of 6 patients analysed with ependymomas 3 were male (50%) and 3 female (50%). The age of the patients analysed was between 15 months and 160 months, and the average age was 48 ± 55 months. Post-surgery, the patients were followed up

for between 3 months to 160 months, with an average of 21 ± 22.5 months. The length of duration of symptoms was between 4 days and 120 days, with an average of 53 days. The clinical picture was dominated by signs of increased intracranial pressure and cerebral syndrome. Headaches were present in 5 (83%) patients, vomiting in 4 (66%) patients, ataxia in all 6 (100%) patients and torticollis in one (16%) patient. One girl had gone blind due to long term and extreme hydrocephalus. Of the 6 ependymomas, which developed in the fourth ventricle, 4 (66%) had passed through the Luschka foramen and spread to the cerebellopontine angle, whilst two had spread through the aqueduct of Sylvius towards the third ventricle. At the point of diagnosis one boy (16%) had metastasis in the spinal subarachnoid space. Of the six tumours analysed the pathohistological diagnosis in 2 (33%) was ependymoma (one boy and one girl), whilst in 4 (66%) it was anaplastic ependymoma (2 boys and 2 girls). Five (83%) tumours were between 31 mm and 50 mm, whilst one (16%) tumour was more than 51 mm. None of the tumours had cystic or haemorrhagic components. Hydrocephalus was present in 5 (83%) patients. In order to treat hydrocephalus 1 (16%) patients had ventriculoperitoneal shunt (VPS) implanted pre-surgery, in 4 (66%) an external ventricular derivation (EVD) was implanted pre-surgery. In one (16%) patient, hydrocephalus was treated only by ablation of the tumour. All 6 patients underwent surgery. Total and subtotal resection of the tumour was achieved in 4 patients, whilst it was achieved partially in 2 patients. In one girl who had extreme, long-term hydrocephalus which had caused the loss of sight, and in whom a VPS was implanted pre-surgery, post-surgery a bilateral supratentorial hygroma and retrocerebellary hygroma to the left. In one girl transitory dysarthria, dysphagia and facioparesis of a peripheral type occurred post-

surgery. These deficits withdrew after a few days. In one boy diplopia accompanied by nystagmus occurred post-surgery. The diplopia withdrew after several weeks, whilst the nystagmus persisted to the point of the last evaluation (after two years). Post-surgery, all patients were treated with adjuvant therapy. Immediately after surgery, chemotherapy was applied in three patients (children under 3 years old), whilst in 3 patients, radiation treatment was given alongside chemotherapy. In two patients who were post-surgically treated only with chemotherapy after they reached the age of 3 years, they also received radiation treatment. In one boy who underwent surgery at the age of 18 months (anaplastic ependymoma) a local recurrence occurred after 6 months, accompanied by multiple subarachnoid metastases, which led to his death two months later. No other patients had any signs of recurrence in the period of post-surgical monitoring.

Discussion

Of the total of 78 patients who underwent surgery in the period from 13.01.1992 to 28.12.2001, 50 patients met the criteria for this study. In this period, surgery was performed on 143 intracranial tumours in children, of which 78 (54.5%) were located in the posterior cranial fossa. This ratio is in line with studies published earlier (18, 19). Bruno et al. (19) presented a study of 1350 children with intracranial tumours in which tumours in the posterior cranial fossa accounted for 54.7%. Of these 50 patients, 6 (12%) had ependymomas, which is also in line with previously published studies (3). The ratio regarding the hemispheres was 1:1 in our study, which is in line with earlier studies, whilst some studies, dealing with supratentorial ependymomas, showed boys to be affected more frequently, in a ratio of 1.4:1 (20, 21).

The age of the patients was between 15 months to 160 months, with an average of

48±55 months. The highest incidence of ependymomas is found in the first four years of life (5-7) which may be seen from our analysis, where 5 patients were under 4 years old.

The clinical picture was dominated by symptoms and signs of increased intracranial pressure and cerebellar syndrome, which most often developed gradually. The average duration of symptoms was 53 days, which is similar in the case of medulloblastomas. At the point of diagnosis, 1 (16%) patient had metastasis in the spinal subarachnoid space. This frequency of metastasis in ependymomas is in correlation with other studies, where the percentage was between 11% to 17% (22, 23). It is particularly important to establish the presence or absence of metastasis at the point of radiological diagnosis, because this is an important factor for prognosis. As a result, it is important to perform NMR of the spinal column as well as NMR of the neurocranium, since post-surgery NMR may give false positive results due to the presence of blood and haemostatic substances (Surgical, Spongostan). On the other hand, the presence of metastasis does not demand surgical intervention, in view of the significant post-surgical morbidity and lack of possibility of radical resection, apart from intervention of a palliative nature. Unfortunately, children with ependymomas at the point of diagnosis are often in poor clinical condition, so that it is impossible to undertake pre-surgical diagnosis, and it is recommended that this be done post-surgery, after two to three weeks, when the blood has been resorbed.

Treatment of hydrocephalus related to ependymoma, as with other tumours in the posterior cranial fossa, is controversial. Hydrocephalus was treated pre-surgically with an EVD, with ablation of the tumour in four patients. In one patient it was treated only by ablation of the tumour, whilst one patient had a permanent VPS (16%). Ten to forty per cent of patients (24-26) have per-

manent VPS after surgery for a tumour in the posterior fossa. In treatment of hydrocephalus with tumours in the posterior cranial fossa it is possible to use ventriculocysternostomy (27).

Post-surgical complications were related to the cerebrospinal fluid system and cranial nerve disorders, accompanied by dysphagia, dysarthria and facioparesis of a peripheral type and oculomotricity disturbances. Complications related to the cranial nerves were transient. One patient had persistent nystagmus even after two years. No recurrence of the illness occurred in the monitoring period. Bearing in mind the short time of monitoring and the small number of patients, it was not possible to examine long term survival and later recurrences.

On CT, ependymomas presented as isodense and heterogenic lesions. Haemorrhages were present in 13% of cases, and calcification in 25% to 50%. The take up of the contrast medium was heterogeneous and irregular (28).

Ependymomas present on NMR as isointensive or hypointensive intraventricular lesions on T1 and isointensive or hyperintensive lesions on T2, which contain calcifications and frequently pass through the Luschka or Magendie foramina, compromising the cranio-cervical junction and brain stem. Extension into the cerebellopontine angle is a pathognomic sign. They take up the contrast comprehensively and may be heterogeneous in character.

Intracranial ependymomas are a major challenge in terms of therapy in paediatric oncology. Advances in neuroradiology make better grading and post-surgical monitoring of patients possible, enabling earlier diagnostics of recurrences and dissemination of the disease (22, 29). As a result routine, regular NMR imaging is necessary to discover asymptomatic recurrences and metastases. The ideal period for NMR monitoring has not been defined, but it is most often carried out every six months in the first two years, af-

ter that once a year for three years, and then every other year. Today most modern studies show a clear connection between the presence of post-surgical tumour residue and recurrence. In practice this may be the only significant prognostic factor (21, 22, 29-32).

Treatment of ependymomas assumes surgical resection of the tumour, the use of radiotherapy and chemotherapy. Surgical resection is the first and most important step in treatment of ependymomas, but complete resection is often not possible, especially when they are located infratentorially and infiltrate the brain stem, or are propagating in the cerebellopontine angle. With ependymomas inserted into the brain stem and not showing signs of dissemination, there is a dilemma about how radical to be in removing them. With complete resection, in view of the fact the ependymomas often affect the obex, there is a major risk of sleep apnoea, swallowing difficulties and repeated aspiration of content upon swallowing. In the absence of complete resection, the tumour always recurs sooner or later. There is a similar dilemma when the ependymoma affects the cerebellopontine angle, where dissection of the tumour may lead to lesions of the cranial nerves, loss of hearing and paralysis of face movements. Very often the tumour damages the lower group of cranial nerves and branches of the posterior inferior cerebellar artery (PICA), even though these neurovascular structures look intact to patients at the end of the operation, tracheotomy and nutritive gastrostomy are very often necessary.

Ependymomas are relatively radiosensitive tumours and standard radiotherapy is used in their treatment, along with radiosurgery. Radiotherapy is used in all patients older than 3 years. Due to the severe psychomotor and neuroendocrine disorders caused by radiotherapy, it is not used in children younger than 3 years. Focal radiation assumes the use of a maximum of 45 to 50 Gy at the site

of the tumour (33). Craniospinal radiotherapy is justified in children with metastasis or with tumour cells in the CSF after follow-up lumbar puncture, but its prophylactic use for localized tumours is debatable.

The use of chemotherapy is limited to children under 3 years old, in order to postpone the use of radiotherapy until they are more than 3 years old, and to use for anaplastic ependymomas. The effects of chemotherapy are still debatable. More recent studies focus on the use of chemotherapy for tumours which have been partially or sub-totally resected (34). In patients who have had total resection of tumours, five-year survival is between 67% and 80%, and in patients with partial resection it is between 22% and 47% (35). In patients with local recurrences, repeat surgery is recommended if possible with the use of radiotherapy and/or chemotherapy, if it has not been used before (36). These patients may be candidates for focal retreatment with various radiotherapy modalities, including stereotaxic radiotherapy (37, 38).

Conclusion

The optimal treatment of ependymomas has not yet been clearly defined. Careful analysis of prognostic factors could give the appropriate guidelines for the future. Maximum surgical resection, with the use of radiotherapy and/or chemotherapy, depending on the age of the patient and the histological findings, is the current treatment method of choice for ependymomas.

Authors' contributions:

Conception and design: MZ and DŽK; Acquisition, analysis and interpretation of data: MZ and FER; Drafting the article MZ; Revising it critically for important intellectual content: MZ and SJ.

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