

Management of Thalamic Low Grade Tumours in Pediatric Age Group

MOHAMMED H. NAYEL, M.D.; IBRAHIM M. IBRAHIM, M.D.; MOHAMMED A. ELBELTAGY, M.D.; AHMED S. ABDELMONEAM, M.D. and AHMED R. ISMAIL, M.D.

The Department of Neurosurgery, Faculty of Medicine, Cairo University

Abstract

Background: Most of thalamic tumors are low grade. They have critical anatomical position especially in children's due to adjacent to important structures.

The Aim Study: Is to present the authors' experience in the management of 24 cases of pediatric thalamic low grade tumors.

Patients and Methods: Medical records of 24 pediatric patients with thalamic brain tumors admitted to Children Cancer Hospital during the period from July, 2007 till December, 2014 have been reviewed as regard surgical interference, and chemo-therapy in relevance to tumor size, patients' age, different histopathological subtypes, and patients' presenting symptoms.

Conclusion: Most of thalamic brain tumors are low grade tumors with significant level of morbidity and mortality that require integrated analysis of further studies to achieve better outcome.

Key Words: *Thalamic tumours – Low grade tumor – Pediatric age group.*

Introduction

MOST of thalamic tumors are low grade tumors.

About 2-5% percent of pediatric brain tumors arise in the thalamic region [1,2].

The existing literature that discuss the management of thalamic brain tumors is sparse and usually includes both adult and pediatric cases which make it difficult to focus on the pediatric subset of the tumors arising in this anatomic region [3,4].

Another limitation of the existing literature is that there was no clear distinction between tumors arising in the thalamic region and those arising from other diencephalic structures and basal ganglia nuclei [5,6].

Since that time, management of pediatric thalamic low grade brain tumors was mainly based on their anatomical origin. Tumors were classified into two major groups: Unilateral thalamic and bithalamic tumors [7].

Here we are presenting our experience in management of 24 cases of thalamic low grade brain tumors in pediatric age group of different histopathological types where the plan of management is based mainly on the histological grading of the tumor [8], and clinical presentations of patients.

Aim of work:

Reviewing the management of patients with thalamic low grade tumours. Stating and clarifying that based on clinical presentation, MRI characteristics and understanding surgical anatomy with pathology, it will be possible to assess the most appropriate group of patients in whom different forms of surgery, chemotherapy, or radiotherapy would be beneficial.

Following the different management plans applied for the included studied cases.

Patients and Methods

Twenty four patients with thalamic low grade tumors were included in this study. These patients were admitted and managed in Children Cancer Hospital of Egypt. An informed consent for every procedure or line of management was signed by patient's relatives.

Inclusion criteria:

Patients included are those patients who:

- Were below 18 years.
- Low grade tumors.
- Were presenting with tumors along the thalamus (intrinsic or extrinsic).

Correspondence to: Dr. Ahmed R. Ismail
E-Mail: dr.ahmed.rabea.ar@gmail.com

Exclusion criteria:

- Above 18 years of age.
- Patients with lesions not arising primarily from the thalamus.
- Patients with previous management (whether surgical or non surgical).
- High grade tumors.

All patients were managed as follows:

- History Taking.
- Full Examination.
- Investigations.

Initial management:

All patients with increased intracranial pressure secondary to hydrocephalus had ventriculo-peritoneal shunt inserted.

Surgical management:

- Stereotactic biopsies were taken using the frameless neuronavigation.
- Surgical excision.

Thalamic tumours were approached via transcortical approaches (through the middle temporal gyrus or posterior parietal lobule). Inverted U-shaped incision was located by the navigation with wide base. The scalp flap was reflected as a single layer and then free bone flap was done, opening the dura then cortisectomy was done, then removal of the tumor, and hemostasis then closure of all layers.

Chemotherapy regimen:**Radiotherapy:**

For progressive course of low grade lesions

Follow-up and serial evaluation of the patients:

MRI brain with contrast was done every 3 to 6 months for every patient for detection of any progression or regression of size of the tumors, and for any complications.

Each patient was followed by serial neurological examination, visual acuity assessment and fundus examination for the assessment of neurological outcomes, development of any new neurological deficits, seizures, behavioral changes, or any complications.

Statistical analysis:

Statistical analysis was performed using SPSS software (version 20) and values are expressed in the form of mean \pm standard deviation. Progression free survival was also calculated for low grade tumors (WHO grade I and II) individually.

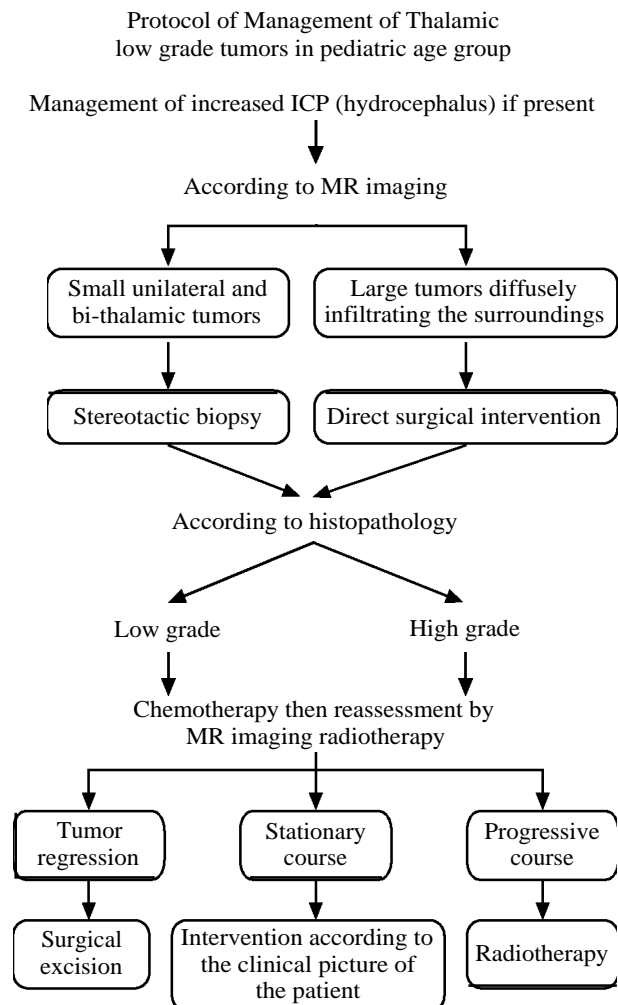


Fig. (1): Algorithm show protocol of management of thalamic tumors in pediatric age group.

Results

By reviewing the medical records of pediatric patients (below 18 years) presented to CCHE with thalamic low grade tumors, we found that 24 patients had thalamic low grade brain tumor.

Among whom 14 were males and the remaining 10 were females with a percent of 58.33% and 41.66% respectively. The patients' ages at presentation range from (1-15 years) with average age 7.5 years.

Eighteen patients (75%) presented by manifestations of increased intra-cranial tension (headache, vomiting, and blurring of vision). Four patients (16.6%) presented by contra-lateral weakness. Two other patients (8.3%) presented by seizures.

Eight patients (33.3%) of the patients who were presented by manifestations of increased intracranial tension developed contralateral weakness later on during the course of the disease.

The two patients with bithalamic tumors presented by symptoms of increased intracranial tension as shown in Table (1) which summarizes both the clinical features and the anatomical origin of the tumors.

Table (1): The anatomical position and clinical features of 33 pediatric patients with thalamic brain tumor.

Presenting symptom	Anatomical site of the tumor		
	Unilateral	Bithalamic	Thalamo-peduncular
Total	20	2	2
Manifestations of increased tension	15	2	1
Contra-lateral weakness	9	1	2
Visual problems	2	1	0
Seizures	1	0	1

All patients with manifestations of increased tension secondary to hydrocephalus underwent ventriculo-peritoneal shunt on the same side of the thalamic lesion (except with few exceptions) in an attempt to relieve the symptoms and decrease the mid-line shift.

MR imaging showed that 22 (91.6%) of the patients had unilateral thalamic tumors while only two (8.3%) patients had bithalamic tumors. Two of the patients with unilateral thalamic tumors had thalamo-peduncular tumors which is a subset of unilateral thalamic tumors which arises at the junction between the thalamus and cerebral peduncles.

One of the two patients with bithalamic tumors had intra-ventricular extension and was presented mainly by manifestations of increased intra-cranial tension and developed also weakness later on during the course of the disease.

The other patient had supra-sellar extension and was presented mainly by symptoms of increased ICP but in contrast to the previous patient, he did not develop weakness. However he had in addition to the previous symptoms left eye proptosis and squint and diminished visual acuity up to counting fingers on right eye and no perception of light on the left eye.

Stereotactic biopsy was performed in 24 (100%) of the patients as a primary diagnostic procedure. The management strategy for the 24 patients is shown in Table (2). According to the histopathological findings obtained through the previous procedures the patients.

Table (2): Different histopathological findings in the 24 pediatric patients with thalamic low grade brain tumors.

Histopathological type	No. of patients with the tumor type	%
<i>Astrocytoma:</i>		
- Pilocytic	10	41.6
- Piloxyoid	1	4.16
- Low grade	2	8.33
- Astroblastoma (well differentiated)	1	4.16
- Ependymoma	3	12.5
Gangliocytoma	1	4.16
Ganglioglioma	6	25
Total	24	100

Low grade tumors:

Twenty-four patients with low grade tumors on histopathology. Twenty-two (91.6%) of those patients with low grade tumors received chemotherapy according to their histopathological findings as an initial line of treatment in an attempt to decrease the tumor size, create plane of cleavage, change the tumor consistency and make it succable during surgery.

The mean age of those patients at presentation was 7.5 years and the mean volume of the lesions at initial MR imaging was 96.5ml. seven patients out of 22 ones (after excluding the two patients who had low grade tumors and underwent direct de-bulking surgeries without stereotactic biopsy sampling) became candidates for surgical interference.

Among those seven patients, five patients underwent total excision and the remaining two underwent subtotal excision as indicated by post-operative MR imaging. All five patients who underwent total excision had completely recovered as regard both clinical features (neurological findings) and radiologic findings with no residual tumor nor recurrences through the period of follow up (mean follow-up duration 3 years and the median 2.25 years).

Those five patients had not received any chemotherapy or radiation therapy during the post-operative period and were only followed-up by MR imaging every 3 months during the first year and every six months during the second year of the follow-up period.

The histological results confirmed that two patients had pilocytic astrocytoma, one patient had

astrocytoma grade II, and two patients had ganglioglioma. The pre and post-operative MR imaging of a patient who underwent total resection.

The two patients who underwent subtotal excision with removal of more than 90% of the tumor had a stationary course of their residuals during the period of follow-up (mean follow-up duration 2.2 years). Histological results confirmed that both patients had pilocytic astrocytoma. They had not received any chemo or radiotherapy exactly as patients with total excision and the residual tumors showed stationary course with no progression during the follow-up period. The pre and post-operative MR imaging of a patient who underwent sub-total excision.

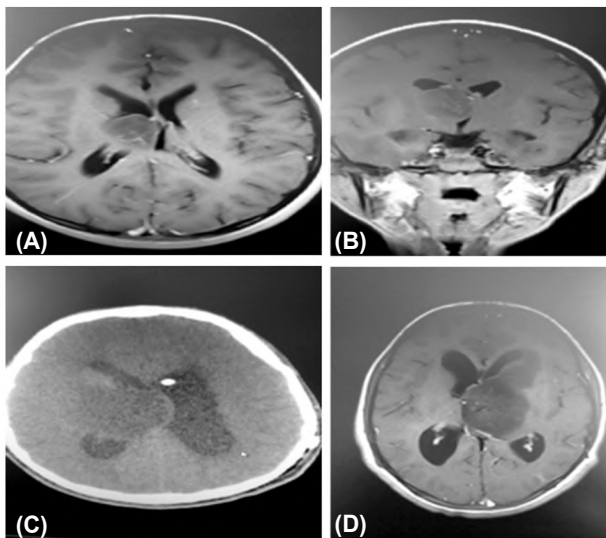


Fig. (2): Showing (A) Axial T1 of preoperative MRI with contrast; (B) Coronal T1 of preoperative MRI with contrast; (C) CT brain after VP shunt and (D) Axial T1 with contrast after six month follow-up. Right thalamic low grade glioma demonstrated in MR imaging obtained in a 15-years-old boy before management. CT brain after VP-shunt. After chemotherapy follow-up MRI not changes.

As an exception to our protocol, two patients were subjected to direct de-bulking surgeries because of the rapidly deteriorating conscious level with severe midline shift on MR imaging. These two patients underwent subtotal excision as indicated by post-operative MR imaging with no neo-adjuvant chemotherapy.

The histological results revealed that both cases were pilocytic astrocytoma. The two patient received adjuvant chemotherapy with no radiation therapy.

One of the patients had a stationary course while the other surprisingly had regressive course

of the residual during the period of follow-up (mean follow up duration was 2.25 years).

The remaining fifteen patients with low grade tumors who found not to be candidates for surgical interference after receiving neo-adjuvant chemotherapy had been followed-up for a mean follow-up duration of 4 years.

Two of them had regressive course of the tumor while being on chemotherapy alone with no need for radiation therapy. One of these two patients had pilocytic and the other had pilomyxoid astrocytomas.

Another six patients had stationary course of the tumors. Two of them had ependymoma and were on both chemo and radiotherapy, whereas the other four patients were only on chemotherapy and had astrocytomas and gangliogliomas. The last seven patients with low grade tumors had progressive course of their lesions despite receiving both chemotherapy and radiotherapy.

Their histopathologic findings showed great variability. Three of them had ganglioglioma, another two patients had pilocytic astrocytoma, while the remaining two patients: One had ependymoma and the other had well differentiated astroblastoma.

Of all the twenty-four patients with low grade tumors who had been followed-up over a period of 3 years (mean follow-up duration), no deaths had occurred. No patient was lost to follow-up.

There was no correlation between patient age at presentation and tumor size and disease outcome.

Whereas statistically significant correlation was found between histological findings and degree of excision from one side and disease outcome from the other side.

Table (3): Summary of different treatment modalities received by the 24 patients with low grade thalamic tumors according to CCHE management protocol of pediatric thalamic tumors.

• Treatment of hydrocephalus by VP shunt in 18 (75%) patients
• Stereotactic biopsy sampling in 22 (91.6%) patients & direct de-bulking surgery in 2 (8.3%) patients
• Neo-adjuvant chemotherapy 22 (91.6%) patients
• Total excision in 5 (20.8%) patients
• Overall treatment
• Chemo only in 8 (33.3%) patients
• Chemo and radio without excision in 7 (29.16%) patients
• Excision and chemo in 9 (37.5%) patients
• Excision, chemo and radio in (0%) patients

Post-operative complications:

Four patients (12.1%) experienced post-operative complications.

Two patient had post-operative deterioration of their conscious level that was improved later one spontaneously with medication and the other with further debulking of the tumor.

Post-operative seizures occurred in one patient. Intracerebral hematoma at tumor bed occurred in one patient which need another surgery for evacuation. During the period of the follow-up four patients need VP shunt revision three proximal and one distal revision.

Another two patients complicated with shunt infection which need EVD and after then reinsertion of the VP shunt.

Neurological outcome:

During the follow-up period three patients had seizures, one of them in the immediate post-operative period and two of them presented initially by fits.

Patient with contralateral weakness improved in five patients, and stationary course in other patients. Other neurological manifestations record including deterioration of level of conscious in one.

Survival outcome:

Event survival rate at 6-months, one and two-years were 100%, 100%, 95.8% respectively. The two-years over all survival rate was 95.8%. One patient died from the progression of the disease.

Discussion

Thalamic tumors in pediatric age group account for about 4% of all intracranial tumors [1]. The management of thalamic low grade tumors in existing literature is mainly based on the anatomical origin of the tumors being classified into 3 main groups: Unilateral, bithalamic tumors and thalamo-peduncular tumors [8].

In this study, the management protocol adopted by our hospital. The main presentation of the patients in this study was the manifestations of increased ICP followed by contralateral weakness. Very few patients were presented by seizures and visual problems which is coinciding with previous literature [7,8].

All patients with thalamo-peduncular tumors had contralateral weakness either as the presenting

symptom or developed later on during the course of the disease due to involvement of the corticospinal tract which is also consistent with existing literature [9].

It is also important to note that not all thalamic lesions are neoplastic especially bilateral thalamic lesions which could be either encephalitis or metabolic diseases [10].

This necessities to confirm the neoplastic nature of these thalamic lesions before administering any harmful adjuvant therapy which is performed by MR spectroscopy. If the lesions where found to be neoplastic in nature, stereotactic biopsy was then performed to confirm the diagnosis and to identify the pathology. In this series the two cases with bithalamic tumors were found to have low grade tumors.

One patient had ganglioglioma and the other had low grade astrocytoma. No further surgical intervention was performed in those two patients other than stereotactic biopsy. Both patients received chemotherapy only according to their pathologies.

One of them had stationary course as regard the tumor size while the other one unfortunately had tumor progression during the period of follow-up. It was difficult to expose this patient with progression to radiation therapy due to its very young age (1.5 year). None of the two patients died during the period of follow-up (the mean follow up duration for those two patients was 2.8 years) which is considered an improvement in the survival compared to existing literature where patients usually die before two years even though being of low grade [2,11,12,13,14].

Stereotactic biopsy (3 biopsy bits) was used as a primary diagnostic procedure in nearly all cases (with exception of the two cases who were subjected to direct de-bulking surgeries as a result of rapid deterioration of the conscious level of the patients with severe midline shift on neuroimaging), as a safe procedure (associated with low morbidities and very low mortality) with high diagnostic yield [15,16,17].

Stereotactic biopsies were taken using the frameless brain lab guided navigation system. A small linear incision and burr hole were done after localization was done by the navigation system.

All patients with low grade tumors received neo-adjuvant chemotherapy (except the two patients who underwent direct de-bulking surgeries) accord-

ing to their pathologies. The aim of neo-adjuvant chemotherapy is to reduce tumor size and vascularity, change the tumor consistency and to create a plane of cleavage. By reducing the tumor size and creating a plane of cleavage, we are increasing the chances of gross total resection. Whereas by devascularizing the tumor, we are reducing the risk of intra-operative blood loss and thus decreasing dramatically the peri-operative morbidity and mortality and reducing the needs for blood transfusion [18].

The chemotherapy regimen included Induction phase (carboplatin/vincristine for 10 weeks - Except for week 5 and week 6 which contains vincristine only). This was followed by Maintenance phase after 2 weeks rest. The later phase consisted of 8 cycles of weekly vincristine/carboplatin for three weeks followed by carboplatin at week 4 with 2 weeks rest between each cycle.

This chemotherapy used with low grade protocol for low grade tumors after stereotactic biopsy.

In this group of patients, the extent of resection was found to be a strong predictor of the patient outcome as indicated by multivariate analysis. All patients who underwent total resection of their tumors after receiving the neo-adjuvant chemotherapy with no further post-operative treatment had completely recovered with no evidence of residuals or even recurrences during the period of follow-up. The effect of extent of resection on the disease outcome has been described before in pediatric patients with thalamic brain tumors [8].

Whereas patients who underwent sub-total resection after receiving neo-adjuvant chemotherapy had either stationary course or even regression of their residual lesions during the period of follow-up while being on adjuvant chemotherapy. This implies that total resection or even subtotal resection should be attempted in every patient with low grade tumor if possible as long as this gross total resection is associated with favorable prognosis.

Among patients with low grade tumors who were not candidates for surgery (15 patients) even after receiving neo-adjuvant chemotherapy, 2 patients had regressive course of their tumors while being only on chemotherapy. Another 6 patients had stationary course of their tumors while being on chemotherapy with the 2 patients with ependymoma having additional radiotherapy.

The remaining 7 patients had progression of their tumors while being also on chemotherapy, so additional radiotherapy was added to 5 patients in

an attempt to control the tumor progression but with unfortunate failure.

From the previous results of the patients with low grade tumors who did not undergo surgeries and were only on chemotherapy without radiotherapy (6 patients), we found that all these patients had favorable prognosis suggesting a strong correlation between the disease outcome and the histological grading of the tumor which is supported by existing literature. Also we found that among the patients with low grade tumors who received radiotherapy (7 patients), 5 patients had disease progression suggesting that irradiation may induce tumor transformation.

Conclusion:

Thalamic brain tumors in pediatric age group are mostly low grade pilocytic astrocytoma. They usually present by manifestations of increased intracranial tension and/or contralateral weakness. According to their anatomical origin in the thalamus indicated by MR imaging they can be classified into three types; thalamo-peduncular, bithalamic and unilateral tumors.

Thalamo-peduncular tumors usually present by contralateral weakness due to compression and stretching of pyramidal tract fibers in the cerebral peduncles.

Bithalamic tumors should be established and confirmed first by means of MR spectroscopy and stereotactic biopsy before starting any harmful adjuvant therapy. Surgery has limited role in management of bithalamic tumors.

Unilateral tumors diagnosed by stereotactic biopsy as a primary minimally invasive diagnostic procedure.

Tumors that were found to be of low grade on stereotactic biopsy, were managed by neo-adjuvant chemotherapy in an attempt to reduce the tumor size and vascularity. This markedly participated in reducing perioperative morbidity and mortality.

Two factors were found to affect the patients' outcome; histological grading of the tumor and radicality of surgery. Surgical excision for high grade tumors does not that much affect the outcome compared to low grade tumors where it significantly affects the outcome.

Radiotherapy should used in patients with progressive low grade tumors and malignant high grade tumors. Irradiation therapy is strongly suggested to be an induction factor for tumor transformation which needs further investigation.

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الطرق المختلفة لعلاج أورام المهاد الحميدة عند الأطفال

معظم أورام المهاد عند الأطفال عادة ما تكون أورام حميدة وهي تمثل نسبة 2-5% من أورام المخ، ويأتى المريض عادة بأعراض زيادة ضغط المخ مثل الصداع المستمر، عدم وضوح الرؤية، الترجيع المستمر. وذلك نتيجة وجود استسقاء بالمخ نتيجة ضغط الورم على البطين الثالث بالمخ ويحتاج المريض لتثبيت صمام مخى بريتونى وذلك لتقليل ضغط المخ.

بالإضافة إلى الأعراض الأخرى مثل ضعف الأطراف وخصوصاً بالجهة العكسية بالجسم من الورم. هذه الأورام إما أن تكون على ناحية واحدة من المخ، أو على الناحيتين، أو تكون لها اتصال بدعامات المخ. هذه الأورام التي لها اتصال بدعامات المخ عادة ما يكون هناك ضعف بالأطراف عند المرضى وذلك نتيجة الشد على مجموعة الألياف العصبية الهرمية بالمخ.

تشخيص الأورام المتواجدة على الناحيتين عادة عن طريق الرنين المغناطيسى الطائفي، أو عن طريق أخذ عينة بالجهاز الملاحي وذلك قبل ما نبدأ العلاج المساعد من العلاج الكيماوى أو العلاج الإشعاعى. أما تشخيص الأورام المتواجدة على ناحية واحدة عادة ما سيكون عن طريق أخذ عينة عن طريق الجهاز الملاحي. معظم الأورام تكون أورام حميدة ويتم علاجها على حسب حجمها لو صغيرة وداخل المهاد تعالج بالعلاج الكيماوى المخصص للأورام الحميدة وذلك لتقليل حجم الورم وتقليل الأوعية الدموية المغذية له. ثم يعاد تقييم المريض للتدخل الجراحى. أما لو كان هذه الأورام الحميدة كبيرة وخارج المهاد ويتم التدخل الجراحى المباشر للاستئصال ثم العلاج المساعد من العلاج الكيماوى والعلاج الإشعاعى.

هذا البروتوكول فى العلاج أدى بشكل كبير إلى تقليل المضاعفات المرضية، والوفيات بشكل ملحوظ وخصوصاً عن الأبحاث الأخرى.

وهدف الدراسة: هو تحديد تلك الوسائل العلاجية وطرق استخدامها وتأكيد فائدتها وإلقاء الضوء على استخدامها.