Management of Posterior Fossa Medulloblastoma in Adults

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Received: 09 / 09 /2010 - Accepted: 12 / 12 /2010.

ABSTRACT

Background: *Medulloblastoma is a malignant tumor of the cerebellum that occurs predominantly in children. It is rare in adults and accounts for less than 1 % of all adult primary brain tumors.*

Objective: *This study was done to study clinical picture, radiological findings, to evaluate the surgical outcome and to assess the effects of postoperative adjuvant therapy in 12 adult patients who had posterior fossa medulloblastoma*

Methods: *This prospective study was carried out on consecutive 12 adult patients who had posterior fossa medulloblastoma. This study was done in Alexandria hospitals over a period of 3 years starting from March 2006 to March 2009. The male to female ratio was 2 to 1(8 males and 4 females) and their ages ranged from 19 to 51 years with mean age of 33, 8 years. Headache was the most frequent symptom (93,5% of patients). As regards the clinical presentation, manifestations of increased intracranial pressure was found in 10 patients (83,3%), cerebellar dysfunction in 8 patients (66,6%), cranial nerve deficits in half of the cases. The tumour was hemispheric in 10 cases (6 lateral and 4 paramedian) and vermian in 2 cases. All patients had preoperative craniospinal MRI examination. No distant or spinal metastases were detected in our patients at the time of diagnosis. All cases underwent surgery in the form of resection of the tumour followed by postoperative craniospinal irradiation. Also two patients with recurrence and metastases received ad-juvant craniospinal radiotherapy and systemic chemotherapy. Mean postoperative follow up period was 24 months, including both clinical and MRI examination.*

Results: *There were no operative mortality, and surgery did not provoke any permanent neurological aggravation. Postoperative MRI studies showed complete tumour resection was achieved in 9 patients (75%). After initial treatment only two patients relapsed in the posterior fossa after one and half year. Recurrence was probably related to incomplete tumor resection and long delay in initiating radiotherapy (3 months after operation). Two of the patients that received adjuvant treatment died: one from distant metastasis and one from recurrent disease. Ten patients remained alive and disease-free with Karnofsky performance status ranging from 80 to100.*

Conclusion: *Adult medulloblastoma was predominant in males and the majority of patients had hemispheric cerebellar tumors. Adults are more likely to have heterogeneous cerebellar tumours on MRI, and this is thought to be related to the greater prevalence of desmoplastic variant in adulthood. Long-term survival was not uncommon. The outcome depends on the site of the tumour with better results obtained in cases with lateral hemispherical tumour that facilitate its complete surgical resection and good irradiation planning.*

Key words*: Adult Medulloblastoma; Posterior Fossa; Craniospinal Irradiation; Desmoplastic Type.*

INTRODUCTION

Medulloblastoma is a malignant invasive embryonal tumor of the cerebellum that occurs predominantly in children with a high tendency to present metastasis at diagnosis.[1] It is rare in adults and accounts for less than 1 % of all adult primary brain tumors.[2] It occurs in the third and fourth decade and has subtle radiological and histological differences from childhood tumor. A hemispheric location is more common in adults and the close proximity to dura gives it a few preoperative extra-axial imaging characteristics. Classic medulloblastoma (CM) and desmoplastic medulloblastoma (DM) are the most common histological variants.[3] Some differences in the presentation, prognostic factors and outcome between adults and children and between CM and DM raised the question whether there are specific features of adult or desmoplastic medulloblastoma.[3,4] Many series of adult medulloblastoma have been reported.[5-7] Most of them were relatively small and collected over long intervals.[5,8,9]

The aim of this work was to study the clinical picture and the radiological findings in 12 adults with posterior fossa medulloblastoma. Also to evaluate the surgical outcome and to assess the effects of postoperative adjuvant therapy in those patients.

METHODS

This prospective study was carried out on consecutive 12 adult patients who had posterior fossa medulloblastoma. This study was done in Alexandria hospitals over a period of 3 years starting from March 2006 to March 2009. The male to female ratio was 2 to 1(8 males and 4 females) and their ages ranged from 19 till 51 years with mean age of 33, 8 years.

Headache was the most frequent symptom (91, 4 % of patients). Other common symptoms, probably due to raised intracranial pressure such as nausea,

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pISSN: 1110-0834
eISSN: 2090-2948

vomiting, blurred vision, and mental changes were found in 10 patients (83, 3%). Ataxia was the second most common symptom. Other cerebellar dysfunctions were found in 8 patients (66, 6%) such as nystagmus, dysmetria and dysarthria. Symptoms referable to cranial nerve deficits included facial weakness, hearing loss; vertigo, tinnitus, and difficult swallowing were found in half of the cases. Abnormal neurological findings at diagnosis are listed in table I. Hydrocephalus was present in 4 cases (2 vermian and 2 paramedian tumours) and was treated by permanent V-P shunt in 2 cases with partial tumour resection.

All patients had preoperative craniospinal MRI examination. Other imaging procedures like CT abdomen + chest and radioisotope bone scan were done. The tumour was hemispheric in 10 cases (6 lateral and 4 paramedian) and vermian in 2 cases. All patients had no distant or spinal metastases at the time of diagnosis.

All cases underwent surgery in the form of resection of the tumour through suboccipital craniectomy (retro sigmoid approach in 6 cases and midline approach in 6 cases) followed by postoperative craniospinal irradiation (median irradiation dose for craniospinal axis was 36 Gy delivered in 20 fractions and 18 Gy for posterior fossa delivered in 10 fractions).

All the patients included were followed-up postoperatively with regular clinical and neuroimaging (CT or MRI) examinations. The last follow-up clinical and MRI examinations were done at a period ranged from 18 to 36 months (mean = 24 months). Progression free survival was estimated with Kaplan-Meier method and comparable tests were performed with long-rank test. Summary data of our 12 patients are listed in table II.

Table I: Clinical features in 12 adult patients with medulloblastoma

Clinical features	Cases	
	No.	Percent
Increased intracranial pressure	10	83,3
Cerebellar dysfunction	8	66,6
Cranial nerve deficits	6	50
Paresis	2	16,6

Most patients had multiple symptoms.

RESULTS

On MRI examination all tumours (100%) were heterogeneous, giving predominantly low or isointense signal on T1 and isointense signal on T2-weighted images. Cystic or necrotic areas in all patients were particularly visible on T2-weighted images. Contrast enhancement was heterogeneous in all cases except one case with no enhancement. Medulloblastomas were hyperintense on diffusion-weighted imaging and had apparent diffusion coefficient. Moreover, in proton magnetic resonance spectroscopy (MRS), they characteristically showed a small taurine peak detectable at short echo time, had an elevated choline peak, and a decreased N-acetyl aspartate peak. Postoperative MRI studies showed complete tumour resection was achieved in 9 patients (75%). Desmoplastic variant was observed in 10 cases (83,3%) including one of the two vermian tumours.

Clinical improvement was obvious in all patients. Patients with increased intracranial pressure respond well to surgery with complete resolution in 80% of cases (8 cases out of 10). Cerebellar dysfunctions markedly improved in 75% of cases (6 cases out of 8).On contrast only 50% of patients with cranial nerve deficits and with paresis of lower limbs improved after surgery.

Postoperative morbidity and mortality: There were no operative mortality, and surgery did not provoke any permanent neurological aggravation. Postoperative CSF leak occurred in two cases that stopped with conservative measures. One patient had severe postoperative headache, lasting for seven days after surgery. Another patient had postoperative meningitis that responded well to medical treatment.

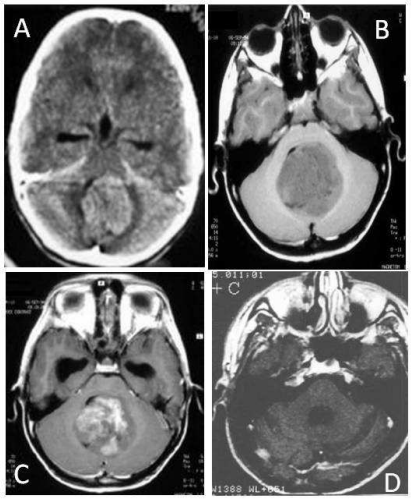
Functional status was evaluated using the Karnofsky disability scale. After surgery all the patients were independent (Karnofsky score > 70). Ten patients remained alive and disease-free with Karnofsky performance status ranging from 80 to 100.

Recurrences and outcome of cases: Two patients experienced recurrent medulloblastoma in posterior fossa at 16 and 18 months from initial treatment. One of them had extracranial metastases in long bones. They were treated by various modalities, including radiation and chemotherapy. None of them is still alive. Recurrence was probably related to incomplete tumour resection plus long delay in initiating radiotherapy (3 months after operation). No patient presented with late treatment-related complication.

Progression free survival was estimated from the date of surgical resection until the date of tumor progression and it was 83% at two years. We did not perform statistical analysis of prognostic factors du to low frequency of recurrences or deaths in our series.

Table II: Summary data for our twelve patients.

No	Age	Sex	Tumor site	Clinical presentation				MRI contrast enhancement	Surgery	Pathology	Adjuvant Therapy		Outcome (Karnofsky disability scale) and follow up period in months	
				↑ICP	Cranial nerve deficits	Cerebellar dysfunction	Paresis				Radio-therapy	Chemo-therapy	Preoperative	Postoperative
1	51	M	Vermian	+	+	+		Heterogeneous	Partial resection	Desmoplastic	+	+	70	0 18 months
2	19	F	Vermian	+	+		+	Heterogeneous	Total Resection	Classical	+		70	80 24 months
3	32	M	Hemispherical Para-median	+	+		+	Heterogeneous	Partial resection	Classical	+	+	80	0 20 months
4	36	F	Hemispherical Para-median	+		+		None	Total resection	Desmoplastic	+		70	80 24 months
5	28	M	Hemispherical Para-median			+		Heterogeneous	Total resection	Desmoplastic	+		80	90 30 months
6	41	M	Hemispherical Para-median	+		+		Heterogeneous	Total resection	Desmoplastic	+		80	90 20 months
7	24	M	Hemispherical lateral	+	+			Heterogeneous	Total resection	Desmoplastic	+		80	100 24 months
8	38	M	Hemispherical lateral		+	+		Heterogeneous	Total resection	Desmoplastic	+		80	100 18 months
9	38	F	Hemispherical lateral	+	+			Heterogeneous	Partial resection	Desmoplastic	+		70	80 30 months
10	42	M	Hemispherical lateral	+		+		Heterogeneous	Total resection	Desmoplastic	+		80	100 36 months
11	24	M	Hemispherical lateral	+		+		Heterogeneous	Total resection	Desmoplastic	+		80	100 22 months
12	33	F	Hemispherical lateral	+		+		Heterogeneous	Total resection	Desmoplastic	+		80	90 25 months



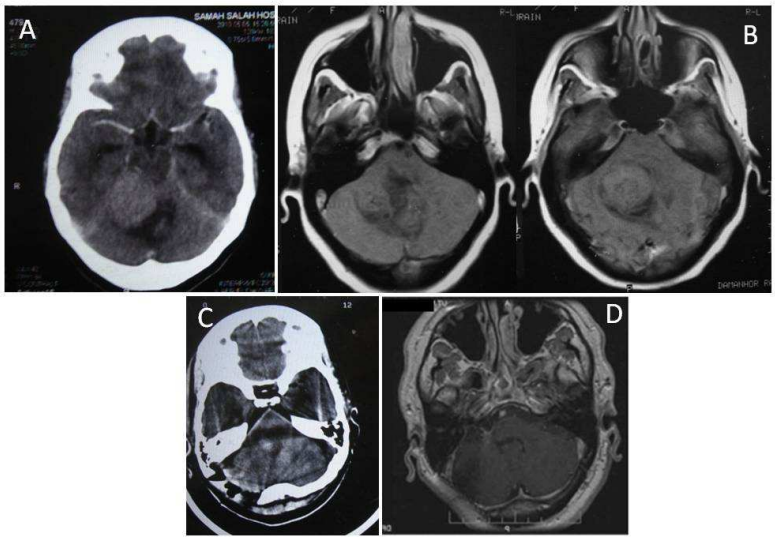
Case I: case of vermian medu1lo blastoma

A) Post contrast CT showing a vermian lesion with a small amount of surrounding vasogenic edema exerting mass effect on the fourth ventricle, with a moderate degree of hydrocephalus.

B) Axial MRI T2-flair image of a case of the same lesion.

C) Axial MRI T1-weighted image with gadolinium showing a heterogeneous enhancement of the lesion.

D) Post operative axial MRI with gadolinium showing complete resection of the lesion with normal appearance of the 4th ventricle.



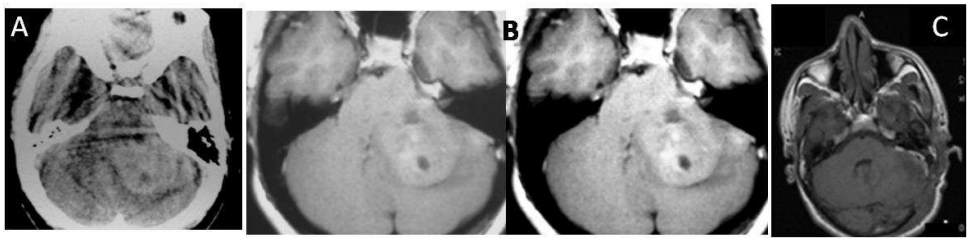
Case II: case of paramedian hemispheric medulloblastoma

A) Post contrast CT scan showing a right cerebellar lesion with a surrounding vasogenic edema exerting mass effect on the fourth ventricle, with hydrocephalus.

B) Axial MRI T1-weighted image with gadolinium of the same lesion with homogeneous enhancement.

C) Immediate psot operative CT scan showing complete resection of the lesion with minimal blood collection n the tumor bed.

D) Post operative axial MRI T1-weighted image with gadolinium showing complete resection of the lesion.



Case III: case of lateral hemispheric medulloblastoma

A) Post contrast CT scan showing a left cerebellar lesion.

B) Axial pre and post contrast MRI T1-weighted image of the same lesion with hetrogenous enhancement.

C) Post operative axial MRI with gadolinium showing complete resection of the lesion.

DISCUSSION

Medulloblastoma originates from primitive or pluripotential cells of the neuron-epithelial roof of the fourth ventricle which normally migrate towards the external layer of the cerebellar cortex. The tumour can develop anywhere along the path of migration.[10] Medulloblastomas in children are usually located in the vermis. In contrast, about half of the medulloblastomas in adults are primarily located in the cerebellar hemisphere.[11] Desmoplastic histological type of medulloblastoma is more common in adults than the classical type. It occurs more often in the lateral cerebellar hemisphere than the classic medulloblastoma.[5,10] Metastases usually occur in the spinal and sometimes the cerebral subarachnoid space.[12,13]

Like the previously published series,[14-16] adult medulloblastoma in our study was predominant in males (75%), and initial clinical presentations included manifestations of increased intracranial pressure, cerebellar dysfunction and cranial nerves deficit.

The majority of our patients (83,3%) had hemispheric tumours like other series.[14,15,17] Although a hemispheric location, particularly lateral tumours, has been previously related to better outcome [18,19] in that they could be more amenable to gross total resection, only one of our patients with lateral hemispherical tumour had partial resection due to high vascularity of the tumour.

Desmoplastic variant was predominant in our patients (83, 3%) and occurred in any of the three possible locations (vermian, paramedian, lateral) as described by Hubbard et al.[17] Desmoplasia was found to be more frequent in adults [21] and also in hemispheric location.[20,21] It is believed to be related to a better prognosis by some authors, [20,22,23] while worse by others.[24,25] Our two patients who relapsed had desmoplastic and classical variants respectively.

There are no pathognomonic MR imaging features of cerebellar medulloblastoma in adults, but tumours are more heterogeneous than in children with frequent evidence of cystic and necrotic degeneration.[20] Small cystic or necrotic foci were present in all our patients in variable numbers. This has also been described in previous series, in from 25% [19] to 82 % [22] of cases. We believe this could be an important feature in the differential diagnosis of medulloblastoma in adults, given that it is not common in the other intraparenchymal posterior cranial fossa tumours. The tumours are hypo- or iso- hyperintense on T2- weighted images. All our patients had tumours which predominantly isointense or gave slightly higher signal than grey matter on T2- weighted images. Bourgouin et al. [21] suggested that isointense signal on T2-weighted images could be related to desmoplastic histology, but we also noticed this in our patients with CM. Contrast enhancement was extremely variable, with no distinct pattern in CM or DM. However, the finding of a well demarcated hemispheric tumour mass with mild to moderate enhancement after gadolinium administration is characteristic for medulloblastoma.[26]

Recent reports suggest that proton MR spectroscopy and diffusion – weighted imaging can add information to preoperative differential diagnosis of brain tumours.[27,28] Wilke et al.[29] described reduced mean apparent diffusion coefficients, possibly reflecting the small-cell histology of the tumour, and a high amount of taurine in a child with medulloblastoma.

Some individual prognostic factors have been evaluated in adult medulloblastoma patients. Unlike in childhood medulloblastoma; most of these factors have not been found to be significantly predictive in adults. Male gender was reported to be significantly predictive of worse survival.[30] Authors found 5-year survival rate of 92% in female patients, 40 % in male patients. Tabori et al.[31] reported better survival female patient in adolescents. In our study, we did not find any progression in female patients (2-year progression free survival is 100 % in female patients, 75% in male patients). Age is a very important prognostic factor in childhood medulloblastomas whereas it has not been found to be significantly predictive in adult patients.[20] However, one study reported survival advantage in older patients.[32] In our study, mean survival was 20 months in patients younger than 25years old, 23 months in patients older than 25years old.

Extent of surgical resection has been considered a good prognostic factor by some authors,[20,22,23] while not by the others.[32,33] None of our 9 patients with complete resection had relapse during the follow up period. A larger population will be necessary to assess the significance of these findings.

Some important poor risk factors have been defined in adult medulloblastoma patients(as more than 25% of tumor remaining after resection, brainstem invasion, and tumor cells present in the CSF, or evidence of distant metastases.[21,30] Prados and colleagues[34] evaluated retrospectively poor risk (26 patients) and standard risk (21patients) adult medulloblastoma patients. They found that 5-year overall survival and disease free survival rates significantly differed between the risk groups (overall survival: 81 % vs. 54%; disease free survival: 58%vs 38%). Another study reported better progression- free survival at 5-year in low risk adult medulloblastoma.[26] In this study, 12 adult medulloblastoma patients evaluated who had no distant or spinal metastases at diagnosis.

Primary treatment modality in adult medulloblastoma is tumour resection. Due to the risk

of CSF dissemination, craniospinal irradiation is given postoperatively.[20,22] Good irradiation planning includes rapid initiation of radiotherapy after surgery and optimal dose of irradiation. Chemotherapy is reserved for recurrent or progressive disease.[24] In our study, craniospinal radiotherapy was administered postoperatively to all patients; adjuvant chemotherapy was administered in 2 cases with relapses (16.6%).

Contrary to childhood medulloblastoma, the optimal use of adjuvant chemotherapy is unclear in adults and there are different chemotherapy regimens reported in the literatures.[12,13] Prados and colleagues [34] reported statistically significant survival advantage in patients who received chemotherapy as compared to the patients who did not receive). Although chemotherapy has been well tolerated and may have contributed to improve survival, it doesn't seem to prevent relapses in our two patients. We could hypothesize that the incomplete surgical resection plus the long delay in initiating radiotherapy could be the major causes of our two relapses. Some authors [20,22] also observed better local control associated with a shorter time to complete radiation therapy, Chan et al [22] could not demonstrate that the long treatment interval (time from surgery to the end of radiotherapy) has been associated with poor outcomes.

Long term survival was not uncommon in our series as previously reported.[20,22,23] Late recurrence occurred in two of our patients in the posterior fossa and was relatively frequent in previous series, reemphasizing the need for long follow up period.[20,22]

Conclusion: Adult medulloblastoma was predominant in males and the majority of patients had hemispheric cerebellar tumors. Adults are more likely to have heterogeneous cerebellar tumours on MRI, and this is thought to be related to the greater prevalence of desmoplastic variant in adulthood. Long-term survival was not uncommon. The outcome depends on the site of the tumour with better results obtained in cases with lateral hemispherical tumour that facilitate its complete surgical resection and good irradiation planning. A high index of suspicion for medulloblastomas should be entertained in atypical posterior fossa lesions in adults. A preoperative diagnosis based on clinical assessment, radiological findings and spectroscopic parameters support complete surgical resection. Consequently, a full benefit of adjuvant therapy can be provided.

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