Ependymomas: A clinicopathologic study

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Abstract

Introduction: Ependymomas are glial neoplasms that account for 4-8% of primary CNS neoplasms. Considerable controversy exists with regards to their prognosis and management, owing to their rarity and heterogeneity.

Objectives: To study the clinical and pathologic features of ependymomas and evaluate their important prognostic variables.

Materials and Methods: A 10 year retrospective study was carried out. The age, sex, location, clinical presentation, radiologic findings, microscopy, type of excision and follow up findings were studied.

Results: 168 ependymomas were identified in a total of 6628 biopsies((2.53%). Majority were seen in the second decade (42/168), M:F ratio was 2:1. 15.48% (26 cases) occurred in the supratentorial compartment, 36.92% (62 cases) infratentorially, and 47.61% (80 cases) in the spinal cord. 90% of the intracranial tumors presented with features of raised ICT while patients with spinal tumors had focal motor deficits. There were 146 classic grade II ependymomas(78.5%), most common location being the posterior fossa, 36 myxopapillary ependymomas(17.8%), all seen in the lumbosacral region and 6 anaplastic ependymomas(3.57%). Anaplastic ependymomas were seen supratentorially in children and young adults while the peak of myxopapillary tumours was in third and fourth decades. 105 patients underwent gross or near total excision while in 16 it was partial or subtotal.

Follow up was available in 73 patients. 9 patients died in the immediate post – operative period. Follow up for the rest varied from 3 months to 9 years. Anaplastic ependymomas were associated with a poorer prognosis. In supratentorial and lumbosacral tumours there was no difference in survival between gross total and subtotal excision while in adult infratentorial grade II ependymomas and cervical ependymomas, gross total excision had a better three year survival.

Conclusions: The prognosis of ependymomas is multifactorial and depends on histologic type and extent of surgical removal.

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Introduction

Ependymomas are central nervous system (CNS) tumours arising from ependymal lining of the ventricles and central canal of the spinal cord[1]. In children, they are the third most common CNS neoplasms after astrocytomas and medulloblastomas and arise mostly infratentorially. In adults, their overall frequency is less as compared to other CNS neoplasms. They arise mostly in spinal cord, where they are the most common intramedullary spinal neoplasms.[2] Though most ependymomas are WHO grade I & II neoplasms and the anaplastic variety (WHO Grade III) is rare; their prognosis depends on the location, age and completeness of surgical removal. To clarify the clinical, pathological & treatment characteristics that determine the prognosis and therapeutic recommendations, there is a need to study these tumours.

Aim of the Study

This retrospective analysis was carried out to determine incidence of ependymomas at our institute, study the various histological grades and subtypes of ependymomas with reference to age group, gender, location and to correlate the prognosis with the patient's age, location, histological grade and subtype and type of surgical removal.

Material and Methods

This is a ten years retrospective study carried out at a tertiary care hospital. The tissues were fixed in 10% formalin and submitted for routine histopathological processing after adequate fixation. Paraffin sections were cut at 4 to 6 microns and were stained with routine Hematoxylin and Eosin (H&E) stain. Special stains such as PTAH, Alcian blue etc. were performed wherever necessary. Proliferative index (MiB1) was done in selected cases.

The clinical, radiological, therapeutic data and follow up information was obtained from the patient's original case records.

The anatomic location of the tumor was based on the radiological imaging and operative findings. The tumours were grouped into 3 large categories: a) Supratentorial, b) Infratentorial and c) Spinal. The supratentorial tumors included the tumors arising from lateral and third ventricles, paraventricular tissues as well as those arising from cortex and other rare supratentorial locations. The infratentorial tumors were divided as those arising from cerebellum and those arising from other infratentorial structures. The spinal tumors were divided into divided into 2 groups. The first group includes the tumors arising from cervical and thoracic part of spinal cord and second

group of lumbar and cauda equina tumors. These groups were made because of prognostic implications of the location of the tumor on the patient survival.

The ependymomas were analyzed taking into consideration various parameters like age, gender, location, clinical features, radiological findings, type of surgery, histological features, grading and post-operative survival. They were assigned grade according to the WHO classification of CNS tumors, 4th edition, 2007.

The assessment of surgery was done based upon the completeness of the therapeutic removal. The surgery was graded as 'gross total' when more than 90% of the tumor mass was removed, 'subtotal' when 70-80% and 'partial' when more than 50% of tumor removed. The completeness of the surgery was judged by the postoperative MRI scan.

Results

A total of 6628 CNS tumors were received in the Neuropathology laboratory during the study period. There were 168 Ependymomas, accounting for 2.53% of CNS tumors. The youngest patient was a 2 month old child while the oldest patient was 63 years old. Majority were seen in the second decade (42/168), 82 cases out of 168 occurred before 20 years of age, with incidence of 48.8%. After the 3rd decade, the incidence of ependymoma gradually fell. Table 1 depicts locations of the tumor. 47.61% of the cases were spinal in location. The overall male to female ratio was 2:1 while in the spinal cord, supra and infratentorial locations it was 3.4:1, 1.3:1 and 1.5:1 respectively. Table 2 shows the clinical features of the intracranial and spinal tumours. Headache, vomiting, focal neurologic deficits, backache, imbalance and bowel/bladder complaints were the common symptoms, depending on site. The various histologic types of Ependymomas and their sites are shown in Table 3. Myxopapillary, Classic ependymoma and its variants (cellular, tanycytic, papillary) as well as anaplastic ependymomas were seen.(Fig. 1A-F). There were 124 classic grade II ependymomas, nearly half of which were infratentorial in location. Both the tanycytic ependymomas were cervicothoracic and all Myxopapillary ependymomas were lumbosacral in location. Correlating the grade with age, as seen in Table 4, grade III tumours were seen in the first two decades of life, while Myxopapillary ependymoma (grade 1) was most common in the 3rd and 4th decades. Anapaestic ependymomas were more common in children.

A pre-operative MRI diagnosis was given in 131/168 cases (Table 5). Supratentorial ependymomas were very difficult to diagnose on MRI. They were mistaken for astrocytomas/ oligodendroglioma or just labeled as gliomas. Infratentorial ependymomas were at times diagnosed as medulloblastomas radiologically.

Table 6 shows the microscopic features like cellularity, presence of pseudo rosettes and true rosettes, necrosis, mitotic activity, microvascular proliferation etc., seen in the various histologic grades. The grade I and II tumours including the variants showed a Mib1 proliferative index of less than 5% while the anaplastic ependymomas showed a MiB1 labelling index between 10 - 40%, with a mean of 25%. Table 7 shows the type of surgical excision performed. 105 patients underwent gross or near total excision while in 16 it was partial or subtotal.

Follow up was available in 73 patients. Out of these 9 patients died in the immediate post-operative period and their postmortem was performed. Follow up for the rest varied from 3 months to 9 years. Tables 8 and 9 shows the follow up and survival of patients less than and older than 12 years respectively, with respect to grade, location and type of surgery. Anaplastic ependymomas were associated with a poorer prognosis, in the three cases where follow up was available two died post operatively while one died at 1 year. In supratentorial and lumbosacral tumours there was no difference in survival between gross total and subtotal excision while in adult infratentorial grade II ependymomas and cervical ependymomas, gross total excision had a better three year survival.

Table 1: Location of Ependymoma

	Location*	No. of cases	% of total ependymomas
I	Supratentorial(total)	26	15.48
	1. ventricular 2. frontal 3. temporal 4. parietal 5. occipital 6. thalamus& brain stem	2 10 2 6 2 4	1.19 5.95 1.19 3.57 1.19 2.38
II	Infratentorial(total)	62	36.90
	1. Cerebellum 2. CPA and other posterior fossa structures	55 7	32.73 4.16
III	Spinal cord(total)	80	47.61
	1. Cervico-thoracic 2. Lumbo-sacral	28 52	16.67 30.95
IV	Rare locations	0	0

* The values represent both intra and extra axial tumors
CPA= Cerebello-pontine angle

Table 2: Clinical presentation

	Clinical features	Supratentorial	Infratentorial	Spinal cord		Total
				Cervico-thoracic	Lumbo-sacral	
1	Headache	21	52	2	0	75
2	Vomiting	13	47	0	0	60
3	Visual disturbances	7	7	0	0	14
4	Convulsions	2	4	0	0	6
5	FND motor	8	5	24	37	74
6	FND sensory	0	1	13	9	23
7	Altered sensorium	7	9	0	0	16
8	Cranial nerve invovl-ment	3	2	0	0	5
9	Imbalance	2	17	3	4	26
10	Cerebellar signs	2	11	0	0	13
11	Backache		0	3	34	37
12	Bowel& bladder complaints	2	0	5	23	28
13	Impotence		0	0	1	1

14	Other*	1	0	1	0	2

(FND= Focal neurological deficit) (UL= upper limb) (LL= lower limb)
*One case of spinal ependymoma was associated with Neurofibromatosis-2(NF-2) and intracranial meningioma

Table 3: Histologic type, grade and location of tumors

	Histological type	WHO grade	Supra-tentorial	Infra-tentorial	Spinal cord		Total
					Cervico-thoracic	lumbar	
1	Classic ependymoma	II	21	60	23	20	124
2	Variants of classic ependymoma						
	a. cellular	II	1	0	1	0	2
	b. papillary	II	1	0	2	1	4
	c. clear cell	II	0	0	0	0	0
	d. tanycytic	II	0	0	2	0	2
3	Anaplastic	III	3	2	0	1	6
4	Myxopapillary ependymoma	I	0	0	0	30	30

Table 4: Correlation of Age with grade of tumor

Age groups in years	Grade I	Grade II	Grade III	Total
< 5	0	23	2	25
6-10	1	13	1	15
11-20	9	31	2	42
21-30	8	26	1	35
31-40	9	15	0	24
41-50	3	15	0	18
51-60	1	6	0	7
> 60	0	2	0	2
Total:	30	132	6	168

Table 5: MRI diagnosis

	Site	Total tumors	ependy-moma	Medullo Blastoma	glioma	oligo	astro	neuro fibroma	other	?
1	Supra tentorial	26	4	0	11	2	3	0	0	6
2	Infra tentorial	62	19	21	2	0	1	0	3	16
3	Cervico-thoracic	28	8	0	2	0	8	0	1	9

4	Lumbo-sa-cral	52	39	0	0	0	5	2	0	6

(? = No definite MRI impression available)

Table 6: Histologic features

S. No	Microscopic feature	Grade I (30 cases)	Grade II (132cases)	Grade III (6 cases)	Total (168)
1	Cellularity a. mild b. moderate c. high	 28 2 0	 55 74 2	 0 2 4	 83 79 6
2	Pseudorosettes	20	130	5	155
3	True rosettes	3	50	2	55
4	Mitosis a. occasional b. 1+ c. 2+	 0 0 0	 7 5 0	 0 0 6	 7 5 6
5	Necrosis	6	44	6	56
6	Endothelial proliferation	1	3	4	8
7	Calcification	5	32	3	40
8	Hemorrhage	14	30	3	47
9	Hyalinised areas	12	1	0	13
10	Hyalinised blood vessels	5	6	0	11
11	Microcystic change	6	8	0	14
12	Clear cells	1	4	0	5
13	Chondroid metaplasia	0	2	0	2

Table 7: Type of Surgery

	Type of excision	Supratentorial	Infratentorial	Spinal cord		Total
				Cervico-thoracic	Lumbo-sacral	
1	GTE	11	29	14	37	91
2	NTE	1	8	4	1	14
3	STE	3	4	2	5	14
4	PE	1	1	0	0	2
6	Biopsy	3	3	2	1	9
7	Not available	7	17	6	8	38

GTE - Gross total excision, NTE - Near total excision, STE - Subtotal excision
PE - Partial excision

Table 8: Survival of patients less than 12 years

Site	Supratentorial (n=0)	Infratentorial (n=32)				Cervical (28)		Lumbo-sacral (1)
Grade	-	II(31)		III(1)		II(28)		I(1)
Type of excision	-	GT(12) (fu=9)	ST(4) (fu=1)	GT(1) (fu=1)	ST	GT(18) (fu=5)	ST(2) (fu=1)	-
Post-operative	-	2	-	1	-		-	-
1 Month	-	1	-	-	-		-	-
3 Months	-No follow up		-	-	-	2	-	-
6 Months	-		-	-	-		-	-
1 Year	-	1	-	-	-		-	-
2 Years	-		1	-	-	1	1	-
3 Years	-	2	-	-	-	1	-	-
4 Years	-	2	-	-	-	1	-	-
7 Years	-	1	-	-	-		-	-
3 Year follow up	-	**5**	0	-	-	**2**	0	-

Table 9: Survival of patients >/= 12 years

Site	Supratentorial (n=32)			Infratentorial (n=36)			Cervical (n=18)	Lumbo-Sacral (n=53)			
GRADE	**II (27)**		**III (5)**	**II (34)**		**III (2)**	**II (14)**	**I (36)**		**II (17)**	
Type of surgery	ST (4) (fu=3)	GT (12) (fu=6)	ST (1) (fu=1)	GT (25) (fu=12)	ST (1) (fu=0)	GT (2) (fu=2)	GT (8) (fu=0)	GT (22) (fu=9)	ST (3) (fu=2)	GT (15) (fu=10)	ST (2) (fu=1)
Post op death	1	-	1	2	-	1	-	-	-	0	-
1 Month	-	-	-	-	-	-	-	-	-	1	-
3 Months	-	-	-	4	-	-	-	1	-	2	-
6 Months	-	-	-	3	-	-	No FU	3	-	4	-
1 Year	-	-	-	2	-	1	-	2	-	1	1
2 Years	-	2	-	0	-	-	-	1	-	1	-
3 Years	2	1	-	0	-	-	-	-	1	1	-
4 Years	-	2	-	1	-	-	-	1	1	-	-
6 Years	-		-	-	-	-	-	-	-	-	-
9 Years	-	1	-	-	-	-	-	1	-	-	-
3 Yr. FU	2	**4**	-	**1**	-	-	-	**2**	**2**	**2**	-

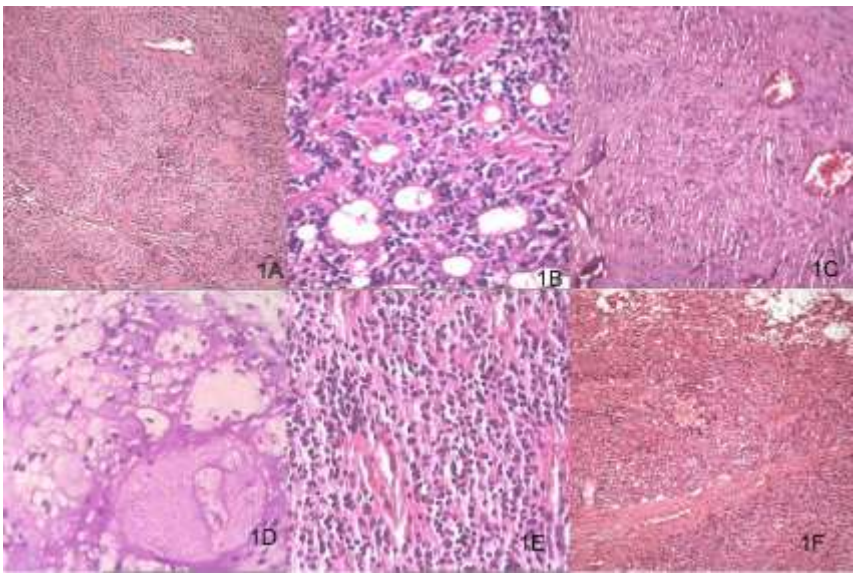

Fig. 1A: Perivascular pseudo rosettes HEx100, 1B: Classic ependymoma with true rosettes HEx400, 1C: Tanycytic ependymoma HEx100, 1D: Myxopapillary ependymoma HEx400, 1E: Cellular grade II ependymoma HEx100, Anaplastic grade III ependymoma with foci of palisaded necrosis HEx100

Discussion

Ependymomas account for 4-8% of primary CNS neoplasms[3] and are more common in children where they account for 8-10% of CNS tumors. Vaishali SS, et al found an incidence of 2.6% in their study on ependymoma in India.[4] Our study comprised of 168 cases of ependymomas, the incidence of ependymomas at our institute was calculated to 2.53% which is in concordance with that reported from India.[4] Ependymomas have a bimodal age distribution with the first peak in childhood & other in middle adulthood.[5] Our study showed that 82 cases (out of 168) occurred before 20 years of age, with incidence of 48.8%. Out of these, 42 were in the second decade (25%). We found that after the 3rd decade, the incidence of ependymoma gradually falls.

For intracranial tumors, male to female ratio is reported as 1.3:1 to 1.5:1 but spinal tumors shows a high male preponderance, M:F = 1.7:1[6,7] We found a gender incidence of 1.3:1 for supratentorial tumors and 1.5:1 for infratentorial tumors. The spinal tumors had a higher male preponderance with male to female ratio of 3.4:1.

Spinal cord ependymomas emerged as most common type of ependymomas accounting for 80 cases (47.61%). 52 cases (30.95%) occurred in the lumbosacral region and 28 cases (30.95%) in the cervicothoracic region. Infratentorial tumors were also common, with 62 cases (36.9%) occurring in the cerebellum & other posterior fossa structures. Supratentorial ependymomas

were relatively uncommon accounting for 15.48% (26 cases). Most supratentorial tumors occurred in frontoparietal region. Spoto GP, et al found 40% of intracranial ependymoma are supratentorial and 60% infratentorial.[8]

Myxopapillary ependymomas occurred exclusively in the lumbosacral region (including cauda equina) of the spinal cord. This finding is in accordance with Kernohan JW, et al who found that 80% of ependymomas at cauda equina are of myxopapillary subtype.[9] The tumors arising from the cervical cord were mostly classic ependymomas, as were those from supra and infratentorial compartments. We found anaplastic ependymomas more common in the supratentorial compartment(3 cases) as compared to the infratentorial compartment(2 cases). This is consistent with finding of Shanop S, et al in their study on supratentorial ependymomas.[10]

The most common clinical symptoms in our study, for supra and infratentorial tumors were headache and vomiting. Out of the 88 intracranial ependymomas, more than 90% had headache and vomiting. Spinal cord tumors mostly presented with motor and sensory deficits in limbs and backache. Lumbosacral tumors also had bladder and bowel function involvement as a common feature, presenting in 44.2% of the lumbosacral tumors. Spinal cord tumors presented with sensory and motor symptoms. One case of spinal ependymoma had clinical features of neurofibromatosis 2 (NF-2). This feature is commonly reported in the literature.[11]Our patient in addition also had an intracranial meningioma.

The accurate diagnostic utility of MRI was found low for ependymomas except for lumbosacral tumors.

All the 168 cases of ependymomas in our study were graded and classified according to the 'WHO classification of CNS tumors, 4th edition, 2007.[3] There were 30 WHO grade I tumors which constituted 17.8% of total cases of ependymomas. They occurred exclusively in the lumbosacral region and correspond to the myxopapillary variant. Data from literature suggests incidence of grade I tumors to be 8-13%.[3,7] Sonneland L, et al in his study on spinal ependymomas, found 27% of spinal ependymomas to be myxopapillary.[7] In our study, this figure was 37.5%.

Grade II ependymomas accounted for 78.5% (132 cases) and they occurred in all the locations- supratentorial, infratentorial and cervicothoracic cord. Vaishali SS, et al also found grade II ependymomas as the commonest type (80.5%).[4] 2 cases of tanycytic ependymoma were seen in our study, both of which occurred in the spinal cord (cervicothoracic). This finding is in concordance with the data in the literature that tanycytic ependymomas have preponderance to occur in spinal cord.[12]

We had only 6 cases (3.57%) of grade III (anaplastic) ependymoma, the incidence in literature varies from 5 - 15%.[1,3] All the cases showed high mitotic activity and palisaded necrosis while microvascular proliferation was seen in 4 cases.

Perivascular pseudorosettes was a common and an important histological feature with 150 cases (89.8%) showing this feature (Fig. 1). True ependymal rosettes, though more specific for ependymomas, were found in only 55 cases (32.73%). (A total of 56 cases (33.3%) showed evidence of necrosis. Small foci of necrosis can be present in all grades of ependymomas and therefore cannot be taken as a histological feature of anaplasia by themselves. Foci of calcification were noted in 40 cases (23.80%). Radiologically foci of calcification can be found in 40% of ependymomas. Areas of hyalinization and hyalinized blood vessels occurred more commonly with myxopapillary ependymomas.

Surgery is the main line of treatment for ependymomas. However complete surgical excision is not possible in many cases of intracranial ependymomas due to proximity of the tumor to the vital structures. 105 patients underwent gross or near total excision while in 16 it was partial or subtotal.

Anaplastic ependymomas had a poor prognosis. Data in the literature has shown variable 5 year survival for supra and infratentorial tumors.[13] Reni M, et al and other investigators found extent of surgery as one of the most significant predictors of outcome in patients with intracranial ependymomas.[14] In the present study, in supratentorial and lumbosacral tumours there was no difference in survival between gross total and subtotal excision while in adult infratentorial grade II ependymomas and cervical ependymomas, gross total excision had a better three year survival.

Conclusion

This study highlights the clinicopathologic profile of ependymomas. Prognosis of this diverse group of tumours appears to be multifactorial.

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