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Original Research Article

Intra-Ventricular Tumors and Their Expression with Immunohistochemistry (IHC) Markers- Original Article

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Abstract: Intraventricular neoplasms of the central nervous system are rare and arise from periventricular structures such as the walls of the ventricular system, the septum pellucidum, and the choroid plexus. Many tumour types arise from, or can bulge into the ventricular system, although there are certain lesions that are relatively restricted to ventricles. A number of factors assist in defining the differential diagnosis, both radiological and clinical, including where the lesion is positioned within the ventricle as well as age and any associated conditions. A total of 30 cases of primary intraventricular tumors were studied. Study included both the left over squash and regular tumor tissue specimen. Duration of the study was 2 years. In this study, the overall incidence of the intraventricular tumors was 5.47 %, 30 cases among the total 548 intracranial lesions. Out of the 30 cases, 19 were males and 11 were females. Most of the cases were seen in the age group of 11 to 20 years and least tumors were seen in the age group 51 to 70 years. Intraventricular tumors are rare tumors and they closely mimic various other tumors of the CNS on imaging. Squash cytology and Histopathological examination (HPE) usually confirms the diagnosis.

Keywords: Intraventricular, Neoplasms, Medulloblastoma, Meningioma, Choroid Plexus Papilloma, Neurocytoma, Glial Fibrillary Acidic Protein, Synaptophysin.

INTRODUCTION

A variety of mass lesions can arise within or in proximity to the ventricular system. These lesions are relatively uncommon, and they present unique diagnostic and surgical challenge. One tenth of all central nervous system neoplasms present within or in proximity to the ventricular system. These neoplasms comprise a heteregenous group with regard to tumor type and clinical prognosis in both children and in adults. Although some of these tumors are aggressive high grade lesions, many are histologically benign and potentially curable by undertaking resections, because they tend to grow slowly, however, they may remain clinically silent and reach significant size before becoming symptomatic , making the excision technically challenging. Typically, these lesions cause symptoms and signs of increased Intra cranial tension (ICT) due to hydrocephalus which will vary depending on the age of the patient ranging from persistent headache or have episodes of vomiting that characteristically occur in the morning. In the nonverbal child the only evidence of increased ICT may be non-specific signs of irritability, loss of appetite or a finding of macro- crania. Specific focal or neurological deficit occur depending on tumor location and

involvement of adjacent structures or surrounding cerebral parenchyma. Primary tumors arise directly from structures within the ventricles. Secondary tumors arise from structures adjacent to the ventricles and grow into the ventricles by extension or invasion. Less than 1% of all intracranial neoplasms arise within the lateral ventricles, although the incidence of lateral ventricular tumors may be higher in the pediatric population. One half of all adult intraventricular tumors and one quarter of pediatric tumors occur in the lateral ventricles. Histological diagnosis varies with both the age of the patient and the specific location of the lesion within the ventricle itself. Micro surgical resections had been the treatment of choice for majority of lesions. Minimally invasive neuro-endoscopic techniques used to diagnose and potentially resects intraventricular tumors may ultimately prove to be as effective as microsurgical approaches. The propensity of intraventricular tumors to reach significant size at presentation as well as the risk of significant bleeding with piece-meal resection, especially in case of lateral ventricular tumors limit the role of endoscopic techniques to selected cases.

AIM OF THE STUDY

To study the histomorphological features of Intra-ventricular tumors and their expression with immunohistochemistry (IHC) markers.

MATERIALS AND METHODS

The study included excision specimen of all intraventricular tumors at the Upgraded Department of Pathology, Osmania Medical College, Hyderabad, Telangana State, India over a two year period from August 2010 to July 2012. Available clinical data including, patient age, sex, Imaging and surgical findings were reviewed from the department of Neurosurgery and the Medical record department, Osmania General Hospital, Hyderabad. A total of 30 cases of primary intraventricular tumors were studied. Study included both the left over squash and regular tumor tissue specimen. All the biopsies were fixed in formalin, embedded in paraffin. Paraffin embedded tissues were examined under light microscopy after

staining with Hematoxylin & Eosin. All tumors were diagnosed on H & E staining and IHC staining with Glial Fibrillary Acidic Protein (GFAP) and Synaptophysin

Inclusion criteria

All Intraventricular tumors, primary and secondary tumors received at the Upgraded department of Pathology from August 2010 to July 2012, with adequate pre operative, intra-operative and post operative information were included in the study.

RESULTS AND OBSERVATIONS

In this study, the overall incidence of the intraventricular tumors was 5.47 %, 30 cases among the total 548 intracranial lesions. Out of the 30 cases, 19 were males and 11 were females. Most of the cases were seen in the age group of 11 to 20 years and least tumors were seen in the age group 51 to 70 years.

Table 1: Sex Distribution Of Intraventricular Tumors

| | No. of Cases | Incidence |
|--------|--------------|-----------|
| Male | 19 | 63.33 % |
| Female | 11 | 36. 67 % |
| TOTAL | 30 | 100 % |

Table 2: Age Distribution

| AGE (IN YEARS) | Number of Cases |
|----------------|-----------------|
| 0 -10 | 5 |
| 11-20 | 7 |
| 21-30 | 5 |
| 31-40 | 5 |
| 41-50 | 4 |
| 51-60 | 2 |
| 61-70 | 2 |
| TOTAL | 30 |

Table 3: Incidence Of The Different Intraventricular Tumors

| Tumor | Incidence (No. of cases) | |
|--|--------------------------|--|
| Central Neurocytoma | 20% (6 Cases) | |
| Astrocytoma | 13.33% (4 Cases) | |
| Colloid Cyst | 10% (3 Cases) | |
| Ependymoma | 6.66% (2 Cases) | |
| Epidermoid Cyst | 6.66% (2 Cases) | |
| Glioblastoma Multiforme(GBM) | 6.66% (2 Cases) | |
| Medulloblastoma | 6.66% (2 Cases) | |
| Neuro-Epithelial Cyst | 6.66% (2 Cases) | |
| Pineocytoma | 6.66% (2 Cases) | |
| Primitive Neuro-Ectodermal Tumor(PNET) | 3.33% (1 Case) | |
| Meningioma | 3.33% (1 Case) | |
| Cysticercosis | 3.33% (1 Case) | |
| Vascular Lesion | 3.33% (1 Case) | |
| Choroid Plexus Papilloma | 3.33% (1 Case) | |
| TOTAL | 100 (30 cases) | |

Most of the tumors encountered in this study were central neurocytoma followed by astrocytoma and least tumors were PNET, Meningioma, vascular malformation and choroid plexus papilloma. Most

common site among the ventricles was lateral ventricles with trigone being the most common area followed by the third ventricle and least cases were seen involving $4^{\rm th}$ ventricle.

Table 4: Predominant Site And Rare Site Among The Ventricles

| SITE | | NO. OF CASES |
|---------------------------|---------------|--------------|
| LATERAL | TRIGONE | 13 |
| VENTRICLES | BODY | 5 |
| | FRONTAL HORN | 2 |
| | TEMPORAL HORN | 1 |
| 3 RD VENTRICLE | | 6 |
| 4 TH VENTRICLE | | 3 |
| TOTAL | | 30 |

Table 5: Gfap And Synaptophysin Expression In Various Intraventricular Tumors

| TUMOR | Cases | GFAP | SYNAPTO-PHYSIN |
|---------------------------------------|-------|--------------|----------------|
| Central Neurocytoma | 6 | Positive – 4 | Positive- 6 |
| | | Negative-2 | Negative-0 |
| Astrocytoma | 4 | Positive – 4 | Positive- 2 |
| | | Negative-0 | Negative-2 |
| Colloid Cyst | 3 | Positive – 0 | Positive- 0 |
| | | Negative-3 | Negative-3 |
| Ependymoma | 2 | Positive – 2 | Positive- 2 |
| | | Negative-0 | Negative-0 |
| Epidermoid Cyst | 2 | Positive – 0 | Positive- 0 |
| | | Negative-2 | Negative-2 |
| Glioblastoma Multiforme(GBM) | 2 | Positive – 2 | Positive- 2 |
| | | Negative-0 | Negative-0 |
| Medulloblastoma | 2 | Positive – 0 | Positive- 2 |
| | | Negative-2 | Negative-0 |
| Neuro-Epithelial Cyst | 2 | Positive – 2 | Positive- 1 |
| | | Negative-0 | Negative-1 |
| Pineocytoma | 2 | Positive – 2 | Positive- 2 |
| | | Negative-0 | Negative-0 |
| PrimitiveNeuro-Ectodermal Tumor(PNET) | 1 | Positive – 1 | Positive- 1 |
| | | Negative-0 | Negative-0 |
| Meningioma | 1 | Positive – 1 | Positive- 1 |
| | | Negative-0 | Negative-0 |
| Cysticercosis | 1 | Positive – 0 | Positive- 0 |
| | | Negative-1 | Negative-1 |
| Vascular Lesion | 1 | Positive – 1 | Positive- 0 |
| | | Negative-0 | Negative-1 |
| Choroid Plexus Papilloma | 1 | Positive – 1 | Positive- 1 |
| | | Negative-0 | Negative-0 |
| TOTAL | 30 | | |

In this study, GFAP and synaptophysin expression was variable and was according to the dominant component in the tumor tissue involving the ventricles. Most of the tumors in this study belong to

the WHO grade 1. This study also revealed that the GFAP expression was more in the Grade 1 tumors when compared to the other tumors.

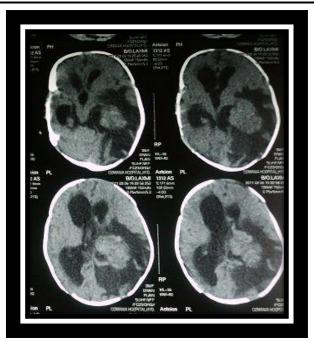


Fig-1: MRI showing mass lesion in the lateral ventricle

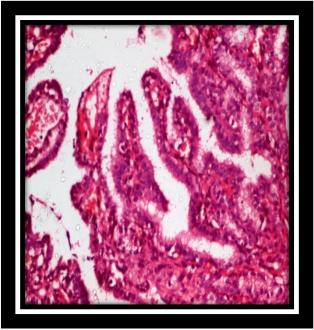


Fig-2: Microphotograph showing papillary pattern of tumor tissue

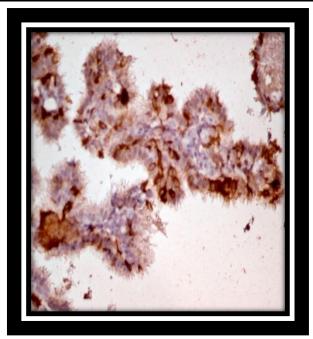


Fig-3: Microphotograph showing GFAP positive- expressed as brown color

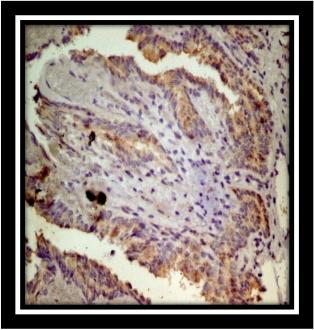


Fig-4: Microphotograph showing Synaptophysin positive- expressed as brown color

DISCUSSION

The brain has several potential spaces or cavities called ventricle which is filled with a clear fluid called cerebrospinal fluid. The cerebrospinal fluid, which also surrounds the brain and spinal cord, helps support and cushion the brain apart from supplying the nutrients to the various cells of the brain. Tumors in the ventricles are known as intraventricular tumors, and they may arise from a variety of cells in and around the ventricular region. The tumors may be astrocytomas, which arise from supporting cells in the brain; meningiomas, tumors of the protective covering of the brain; ependymomas, which arise from the linings of

the ventricles themselves; colloid cysts and craniopharyngiomas, which arise from developmental cells; or other brain tumors. As a whole, intraventricular tumors make up 10 percent of tumors in the central nervous system.

Intraventricular tumors are especially significant because they often lead to obstruction of cerebrospinal fluid flow. When the flow of cerebrospinal fluid is blocked, it leads to a condition known as obstructive hydrocephalus where the volume of fluid in the ventricle increases, placing pressure on surrounding brain tissue and leading to a headache,

nausea, mental status deterioration, visual disturbances, and death. Intraventricular tumors can cause other symptoms depending on location, including seizures, weakness or numbness in the limbs, impairments in language function, gradual changes in mood or personality, and memory loss.

Glial fibrillary acidic protein (GFAP) was named and first isolated and characterized by Lawrence F. Eng in 1969 [1]. In human beings, GFAP gene encodes Glial fibrillary acidic protein (GFAP) [2]. GFAP is expressed by numerous cell types of the central nervous system (CNS) including astrocytes and ependymal cells; it is grouped as intermediate filament protein [3, 4]. According to researchers, GFAP has also been found to be expressed in glomeruli and fibroblasts of peritubular region taken from rat kidneys, Leydig cells of the testis in both hamsters and humans, human keratinocytes, osteocytes and chondrocytes and stellate cells of the pancreas and liver in rats [5-10]. GFAP is thought to provide and maintain mechanical strength to astrocytes and shape of cells; however the exact function still remains poorly understood, despite the number of studies using it as a cell marker. GFAP is expressed in the central nervous system in astrocytes [3, 11]. It is involved in many important CNS processes, including cell communication and the functioning of the blood brain barrier.

GFAP has been shown to play an important role in mitosis by adjusting the filament network present in the cells. GFAP is proposed to play a role in astrocyte-neuron interactions as well as cell to cell communication. In vitro, using antisense RNA, astrocytes lacking GFAP do not form the extensions usually present with neurons [12]. Biochemical studies of GFAP have shown MgCl₂ and/or calcium/calmodulin dependent phosphorylation at various serine or threonine residues by PKC and PKA [13] which are two kinases that are important for the cytoplasmic transduction of signals. These data highlight the importance of GFAP for cell to cell communication. GFAP has also been shown to be important in repair after CNS injury, more specifically for its role in the formation of glial scars in a multitude of locations throughout the CNS including the eye and brain.

Synaptophysin, also known as the major synaptic vesicle protein p38, is a protein that in humans is encoded by the SYP gene [14]. The gene is located on the short arm of X chromosome (Xp11.23-p11.22). It is 12,406 bases in length and lies on the minus strand. The encoded protein has 313 amino acids with a predicted molecular weight of 33.845 kDa the protein is a synaptic vesicle glycoprotein with transmembrane domains weighing 38 kDa. It is present in neuroendocrine cells and in virtually all neurons in the brain and spinal cord that participate in synaptic transmission. It acts as a marker for neuroendocrine tumors, and its ubiquity at the synapse has led to the use of synaptophysin immunostaining for quantification of synapses [15]. The exact function of the protein is unknown: it interacts with the essential synaptic vesicle protein synaptobrevin, but when the synaptophysin gene is experimentally inactivated in animals, they still develop and function normally [16]. Recent research has shown, however, that elimination of synaptophysin in mice creates behavioral changes such as increased exploratory behavior, impaired object recognition, and reduced spatial learning [17] Using immunohistochemistry, synaptophysin can be demonstrated in a range of neural and neuroendocrine including cells the adrenal medulla and pancreatic islets. As a specific marker for these tissues, it can be used to identify tumours arising from them, such as neuroblastoma, retinoblastoma pheochromocytoma, carcinoid, small cell carcinoma , medulloblastoma and medullary thyroid carcinoma, among others.

In reviewing the literature, According to Harjinder S. Bhatoe *et al* [18), Ventricles are rare sites for the occurrence of meningiomas. The incidence of meningiomas of lateral ventricles in adults is variously reported as between 0.5 and 3% of all intracranial meningiomas [19, 20]. In the current study, the incidence of intraventricular Meningioma was reported to be 3.33 % 1 case out of 30 primary intraventricular cases, which is corresponding to the study of Harjinder S. Bhatoe *et al* [18]. In this study, one case of meningioma was reported which was positive for both GFAP and synaptophysin.

In reviewing the literature, according to Pawar SJ *et al* [21], Choroid plexus papillomas are a variety of congenital intracranial tumors of neuroectodermal origin. They constitute about 1% of the total spectrum of central nervous system tumors. The most frequent site of occurrence is the lateral ventricles and sometimes they are multiple in natures. Among these tumors, those originating in the region of the third ventricle are very rare. A small-size tumor in the third ventricle is likely to be missed at a very early stage.

In the current study, only one case of Choroid plexus papilloma was reported at the trigone of the lateral ventricle, which happens to be the most frequent site of occurrence by Pawar SJ *et al* [21]. One case of choroid plexus papilloma (CPP) was reported and was found to be positive for both GFAP and synaptophysin.

In reviewing the literature, according to Lucy B Rorke [22] Intra-ventricular ependymomas constitute 6.16% of all the intracranial neoplasms. According to world health organization (WHO), Intraventricular Ependymomas constitute about 6-12% of the intracranial tumors. In the current study, only 2 cases were reported in the intraventricular region, which constitutes about 6.66 % of all the intracranial

neoplasms. Both the cases showed positivity for GFAP and synaptophysin.

In reviewing the literature, According to Young-Jin Kim *et al* [23], Glioblastoma represents 15%-20% of all intracranial tumors and approximately 50% of gliomas in adults. Although capable of arising anywhere in the CNS, these tumors mainly present as a frontotemporal lesion (63%) of the cerebral cortex. But, intraventricular glioblastoma multiforme (GBM) is relatively rare and is usually found predominantly in the frontal horn or body. In this study, two cases of glioblastoma multiforme (GBM) were reported and both the cases were positive for GFAP and synaptophysin.

In reviewing of literature, Astrocytomas constitute 28.80 % and 3-6% as intraventricular, according to Wahat *et al* in 1981, and 59.90% all neuroepithelial tumors and 6-10% as intraventricular according to Dastur and Lalitha *et al*. In this study, 4 cases were reported and all these 4 cases were positive for GFAP and only 2 cases were positive for synaptophysin.

In reviewing the literature, According to Diane Armao *et al* [24], colloid cysts of the 3rd ventricle are rare lesions comprising of 0.5% -1% of primary brain tumors. In the current study, we reported 3 cases of colloid cysts in the 3rd ventricle and all these three cases were negative for GFAP and synaptophysin.

Central neurocytoma, abbreviated CNC, is an extremely rare, ordinarily benign intraventricular brain tumor that typically forms from the neuronal cells of the septum pellucidum [25]. The majority of central neurocytomas grow inwards into the ventricular system forming intraventricular neurocytomas. This leads to two primary symptoms of CNCs, blurred vision and increased intracranial pressure. Central neurocytomas are rare brain tumors that are located most of the times in the lateral ventricles near the Monro foramina. They were first discovered by Hassoun and co-workers in 1982, and were classified as grade II tumors [26]. In 1985, Wilson had also described a rare case of "differentiated neuroblastoma" in the lateral ventricle that resembles oligodendroglioma on light microscopy. Central neurocytomas predominantly form in young adults, most commonly during the second or third decade of life [27]. There is no evidence that the sex of a person is a determinant in the frequency of central neurocytomas. In this study, we have encountered 6 cases of central neurocytoma, 4 cases were positive for GFAP and 2 were negative. Similarly, all the cases were positive for synaptophysin.

Epidermoids are congenital lesions of epidermal origin, representing 0.2% to 1.8% of all primary intracranial tumors. They arise from epithelial remnants at the time of neural tube closure, between the

third and fifth week of fetal development. Epidermoid cysts occurring within the lateral ventricles are rare. They are slow growing benign tumors usually presenting with nonspecific signs of deterioration of mental functions including recurrent headaches, seizures, paresis, and chemical meningitis, symptoms of fat embolism, olfactory delusion, psychomotor and visual disturbances. Epidermoids grow by the accumulation of keratin and cholesterol, which are the breakdown products of desquamated epithelial cells. In this study, 2 cases of epidermoid cysts were reported and both these cases were negative for the markers GFAP and synaptophysin.

One-half of primary brain tumors in children originate in the posterior fossa. Medulloblastomas are highly malignant tumors; they are the most common malignant posterior fossa tumor in the pediatric population. They are characterized by their tendency to seed along the neuraxis, following cerebrospinal fluid (CSF) pathways, and they represent one of the few brain tumors, including ependymoma, pineoblastoma, and lymphoma, to metastasize to extra-neural tissues. Originally classified as a glioma, medulloblastoma is now referred to as a primitive neuroectodermal tumor (PNET). In this study, we came across 2 cases of medulloblastoma and one case PNET. of Medulloblastoma showed GFAP negative for 2 cases and synaptophysin positive for 2 cases, PNET showed positive for both GFAP and synaptophysin.

CONCLUSION

Intraventricular tumors are rare tumors and they closely mimic various other tumors of the CNS on imaging. Squash cytology and Histopathological examination (HPE) usually confirms the diagnosis. In doubtful cases, Immuno-histo-chemistry (IHC) becomes very useful for definite diagnosis. In this study, we came across variety of intraventricular tumors, most of them being positive for GFAP and Synaptophysin indicating the cell of origin of the tumor.

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