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A CORRELATION OF CLINICOPATHOLOGICAL AND RADIOLOGICAL FINDINGS OF CENTRAL NERVES SYSTEM TUMOURS

Pathology

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KEYWORDS

INTRODUCTION

The annual incidence of tumors of the central nervous system ranges from 10 to 17 per 100,000 persons for intracranial tumors and 1 to 2 per 100,000 persons for intraspinal tumors. Tumors of the CNS account for nearly 20% of all cancers of childhood. Seventy percent of childhood CNS tumors arise in the posterior fossa; a comparable number of tumors in adults arise within the cerebral hemispheres above the tentorium.[1]

Classification of tumors is based on histologic and biologic features, combined with newer molecular analyses. Treatment protocols and experimental trials of glial tumors are usually based on the World Health Organization (WHO) classification, which segregates tumors into one of four grades according to their biologic behavior, ranging from grade I to grade IV.[2]

Paediatric neoplasms occur in the posterior fossa than in the anterior fossa, whereas the opposite is true of adult neoplasms. The WHO sponsors a uniform terminology and grading system of brain tumors, starting with the most benign as grade I, numerical grades II, III, and IV represents increasing severity of malignancy.[2]

Primary brain tumors are diagnosed in approximately 52,000 people each year in the United States. At least one-half of these tumors are malignant and associated with a high mortality rate. Glial tumors account for about 60% of all primary brain tumors and 80% of those are malignant neoplasms. Meningiomas account for 25%, vestibular schwannomas 10%, and CNS lymphomas about 2%. Brain metastases are three times more common than all primary brain tumors combined and are diagnosed in approximately 150,000 people each year.[3]

The current advances in diagnostic and therapeutic modalities have lead to increasing identifications of a variety of CNS neuropathologic processes. This gives rise to urgent need for accurate characterization and localization of space-occupying lesions by cytology and histology.[4]

Most of the patients with neoplasm have fairly characteristic presentation. However, many patients with intracranial masses present a greater diagnostic challenge because of atypical presentation secondary to intratumoral hemorrhage, arterial occlusion and cerebral infarction or tumour involvement of silent areas. In such cases it is important to utilize modern neuro - radiological procedures in order to detect the lesion to localize it and thus predict the histological tumor type.[5]

The 2016 World Health Organization classification of tumors of the central nervous system is both a conceptual and practical advance over its 2007 predecessor. The 2016 edition has added newly recognized neoplasms, and has deleted some entities, variants and patterns that no longer have diagnostic and/or biological relevance.[6]

The present study was undertaken to observe clinical features and frequency of various histologic types of tumours of central nervous system in different anatomic locations at a tertiary care Hospital in South - East Rajasthan.

AIMS AND OBJECTIVES

- To study the spectrum of central nervous system tumors in a tertiary care hospital.
- To histologically grade and classify the CNS tumors according to WHO classification (2016).
- To study gross and microscopic findings of CNS tumors.
- To correlate histopathological findings with clinical features and radiological findings.

MATERIALS AND METHODS

Source of data

The present study was carried out in the Department of Pathology, Geetanjali medical college and hospital, Udaipur. The study included 48 cases of central nervous system tumors received at the histopathology section of the department over one and half year period from January 2017 to June 2018.

Method of collection of data

All central nervous system tumor biopsies were included in the present study. A concise clinical history regarding age, sex, presenting complaints including headache, vomiting, dizziness, seizures, visual field defects, memory loss and cognitive defects with duration of symptoms was taken in the present study along with the physical findings.

CT scan and /or MRI findings were also included in this study.

INCLUSION CRITERIA

All the histologically proved cases of central nervous system tumors were included in the present study.

EXCLUSION CRITERIA

All the non-neoplastic cases of central nervous system were excluded from the study.

Sample size

Sample size was calculated using EPI INFO TM7based on assumption that alpha error to be 5% i.e. confidence level of 95% and beta error to be 20% i.e. power of study 80%. Expected correlation in control was found to be 0.4% with cases. Sample size of 48 cases was included in the study.

Histopathology (post-surgical) specimen/Biopsy Fixation:[7]

The tissue was immediately placed in fixative after surgery. Buffered 10% formal saline was used as a fixative. The solution was prepared as: 40% Formaldehyde - 100 ml, Water (H_2O) - 900 ml, Sodium chloride - 9 gms, Sodium phosphate, dibasic - 12 gms. The volume of formalin taken was 15-20 times the volume of specimen and gross sectioning

was done preferably within 24 hours of surgery of the patient.

Gross examination was done. Specimen: size, colour and consistency, Cut surface: homogenous, heterogenous, solid, haemorrhagic, cystic, necrosis or calcification.

Tissue sections taken from above locations were subjected to routine paraffin processing & staining by hematoxylin & eosin method after giving proper identification number.

Technique of processing[7]
After fixation, routine specimens were processed in an automatic vacuum tissue processor. The specimens were passed first through increasing concentrations of isopropyl alcohol for dehydration, then through xylene for lipid extraction and clearing of alcohol and finally paraffinised in paraffin baths.

Embedding[7]
On completion of processing the tissue basket was transferred to a heated reservoir or free-standing bath of molten paraffin wax.

Tissues were removed from their cassettes, one at a time only, with forceps and placed face down in a steel mould of molten paraffin wax with temperature maintained at 65 degree Celsius, using automated paraffin station.

The mould was placed on a refrigerated surface or ice tray to facilitate the fixation of the tissue to its base. Once the wax was solidified, the tissue blocks were gently removed with their moulds and kept for microtomy.

Section cutting:[7]
A small amount of water was adsorbed into the tissue causing slight swelling, making sectioning easier.

Sections were cut at 3-4 microns by fully automated rotary microtome fitted with disposable low profile steel blade.

The cut sections were floated in a tissue flotation bath at 50 degree Celsius to remove the wrinkles. Then they were picked up on a glass microscopic slide coated with very thin layer of 22% glycerol egg albumin adhesive.

The slides with the cut tissues were placed in a hot oven at 65 degree Celsius for 20 minutes to remove the water between the section and the slide and enabled proper adherence of the tissue on the slide.

Hematoxylin and eosin Staining:[7]
Reagents
1. Mayer's Haematoxylin
This alum hematoxylin is chemically ripened with sodium iodate. It is also useful as a progressive stain, particularly in situations where a nuclear counterstain is needed to emphasize a cytoplasmic component which has been demonstrated, by a special stain, and where the acid-alcohol differentiation might destroy or de-color the stained cytoplasmic component. The stain is applied for a short time (usually 5–10 minutes), until the nuclei are stained, and is then 'blued' without any differentiation.

Preparation of solution
The hematoxylin, potassium alum, and sodium iodate were dissolved in the distilled water by warming and stirring, or by allowing to stand at room temperature overnight. The chloral hydrate and citric acid were added, and the mixture was boiled for 5 minutes, then cooled and filtered.

2. 1% aqueous Eosin Y- Eosin Y (water soluble) - 1 gm, Distilled water 100ml.

3. Eosin - Phloxine B solution- Aqueous 1% eosin Y - 100 ml, 1% Phloxine B - 10 ml, Absolute alcohol - 780 ml, Glacial acetic acid - 4 ml.

Procedure:
1. The sections were dewaxed in two changes of xylene (2-3 minutes) and taken through decreasing grades of alcohol (100% 80% & 70% for 2 minutes each) and then brought to running water.
2. The sections were stained with Mayer's hematoxylin for 8-15 minutes.
3. They were then washed under running water for 10 minutes.
4. They were then stained with eosin for 1 minute and then washed with running water for 2 minutes.
5. They were dehydrated in increasing grades of alcohol (70%, 80% & 100% for 2 minutes each) solutions, followed by clearing in two changes of xylene for 2 minutes.
6. Then finally the slides were mounted with a coverslip by putting a drop of DPX and putting a coverslip over it.

RESULTS
- Cytoplasm-varying shades of pink
- Nuclei - blue
- Muscle, keratin, coarse elastic fibres, fibrin - deep pink/red
- Red blood cells - orange/red
- Collagen, reticulin, connective tissue, amyloid - pink

The slides were examined under scanner, 10x and 40x objective lenses. The central nervous system tumours were diagnosed as per WHO criteria (2016) into diffuse astrocytic and oligodendroglial tumours, ependymal tumours, gliomas, choroid plexus tumours, tumours of the pineal region, tumours of the cranial and paraspinal nerves, meningiomas and metastatic tumours on the basis of histomorphologic characteristics.

The central nervous system tumors were diagnosed and graded as per WHO criteria (2016). Immunohistochemistry was advised in poorly defined malignant neoplasms or when difficulty was experienced in typing the malignant tumours correctly in hematoxylin and eosin stained sections.

Clinico-pathological, radiological correlation and tumor grading was done in all the cases. Statistical analyses were done in the present study.'

RESULTS
Location of the Tumors
We noted that frontal lobe (16 cases, 33.33%) was the most common site of tumor followed by cerebello-pontine angle (5 cases, 10.42%), posterior fossa (4 cases, 8.33%) and tempero-parietal region (4 cases, 8.33%).

WHO grading of CNS tumors
WHO grade I tumors (17 cases, 35.42%) were the most common CNS tumors followed by grade III (11 cases, 22.92%) and Grade IV (11 cases, 22.92%). 4 tumors which were not graded were pituitary tumors and metastatic carcinoma (Table 1).

Table 1: Distribution of various WHO grades in CNS tumors

WHO Grade	No.	%
I	17	35.42%
II	5	10.42%
III	11	22.92%
IV	11	22.92%
No grade	4	8.33%
Total	**48**	**100.00%**

The most common symptom in glioblastoma was headache followed by altered sensorium. Headache was most common symptom in all variants of meningioma. Hearing loss was seen in all 3 cases of schwannoma. All 3 Patients of pituitary adenoma presented with visual field defects.

Table 2: Correlation of age with histopathological diagnosis

	Clinical features							
Diagnosis	**Headache**	**Vomiting**	**Seizure**	**Hearing loss**	**Vertigo**	**Decreased Vision**	**Altered sensorium**	**Memory loss**
Pilocytic Astrocytoma	1	1	-	-	-	-	-	-
Diffuse Astrocytoma	2	-	1	-	-	-	1	-
Anaplastic Astrocytoma	1	2	2	-	-	1	4	-
Glioblastoma	7	4	2	-	-	-	6	2

Anaplastic Oligodendroglioma	5	3	2	-	1	-	1	-
Anaplastic Ependymoma	2	1	1	-	1	-	-	-
Choroid Plexus Papilloma	1	1	-	-	-	-	-	-
Medulloblastoma	2	1	-	-	-	1	1	1
Angiomatous Meningioma	1	1	-	-	-	-	-	-
Fibrous Meningioma	3	1	2	-	-	-	-	-
Meningothelial Meningioma	2	2	-	-	-	-	-	-
Transitional Meningioma	4	2	2	-	1	-	-	-
Atypical Meningioma	2	1	-	-	-	-	-	-
Chordoid Meningioma	1	-	-	-	-	-	-	-
Hemangioblastoma	1	-	-	1	-	-	-	-
Schwannoma	2	-	-	3	2	-	-	-
Metastatic Carcinoma	-	-	1	-	-	-	1	-
Pituitary Adenoma	2	-	-	-	-	3	1	-
Total	**39**	**20**	**13**	**04**	**05**	**05**	**15**	**03**

There were total 15 cases of astrocytoma, among which 8 cases were of Grade IV followed by 4 cases of Grade III. Males were more commonly affected. M:F ratio for astrocytoma observed in this study was 2:1.

Table 3: Grade and sex wise distribution

Grade	Male		Female		Total	
	Astrocytoma	Meningioma	Astrocytoma	Meningioma	Astrocytoma	Meningioma
Grade I	1 (6.67%)	6 (42.85%)	-	5 (35.71%)	1 (6.67%)	11 (78.57%)
Grade II	1 (6.67%)	1 (7.15%)	1 (6.67%)	2 (14.29%)	2 (13.33%)	03 (21.43%)
Grade III	3 (20%)	-	1 (6.67%)	-	4 (26.67%)	-
Grade IV	5 (33.33%)		3 (20%)		8 (53.33%)	
Total	10 (66.67%)	7 (50%)	5 (33.33%)	7 (50%)	15 (100%)	14 (100%)

Grade I meningiomas were most common meningioma comprising of 11 cases (78.57%). Grade II meningiomas comprised of 03 cases (21.43%). Males and females were equally affected by meningiomas, both comprising of 7 cases each.

Diagnostic accuracy of MRI/ CT scan v/s Histopathological diagnosis in the present study

Among the 22 cases of glioma, 21 cases were diagnosed correctly in the CT/ MRI scan. One case of glioblastoma (confirmed on histopathology) was misdiagnosed as meningioma. Hence the diagnostic accuracy of Gliomas was 95.45%. 3 cases of embryonal tumors were diagnosed correctly on CT/MRI scan. All the 14 cases of meningioma were diagnosed correctly on CT/ MRI scan. Choroid plexus papilloma (confirmed on histopathology) was misdiagnosed as schwannoma on MRI scan. Histopathological diagnoses of schwannomas (3 cases) were consistent with the radiological diagnoses of schwannomas. All 3 cases of pituitary adenoma were correctly diagnosed on MRI scan. Hence out of total 48 cases, 46 cases were diagnosed correctly on CT/ MRI scan. Total diagnostic accuracy was 95.83%.

Table 4: Correlation of histopathological diagnosis with radiological diagnosis in the present study

Diagnosis	Total no. of cases in Histopathology	True positive on Radiology	Misdiagnosed on Radiology	Diagnostic Accuracy
Gliomas	22	21	01	21/22 (95.45%)
Embryonal Tumors	03	03	00	03/03 (100%)
Choroid Plexus tumors	01	00	01	00/01 (0%)
Meningioma	14	14	00	14/14 (100%)
Tumors of cranial and paraspinal nerves	03	03	00	03/03 (100%)
Hemangioblastoma	01	01	00	01/01 (100%)
Pituitary neoplasm	03	03	00	03/03 (100%)
Metastatic carcinoma	01	01	00	01/01 (100%)
Total	48	46	02	46/48 (95.83%)

DISCUSSION

The present prospective study comprised of 48 cases of CNS tumours received in the department of Pathology, Geetanjali Medical College and Hospital Udaipur from January 2017 to June 2018.

Age distribution

The peak incidence of CNS tumors in the present study was in the fifth decade (16 cases, 33.33%) which was similar to the observations of Pradhan et al (2017)8 who reported the highest number of patients among 41-50 years (38 cases, 29.23%). However, Masoodi et al (2012)[9], reported the highest incidence of CNS tumors in age group 31-40 years.

Authors (year)	No. of cases	0-10 years	11-20 years	21-30 years	31-40 years	41-50 years	51-60 years	>60 years
Masoodi et al (2012)	106	03 (2.83%)	10 (9.43%)	08	26 (24.52%)	24 (22.64%)	18 (16.98%)	17 (16.03%)
Pradhan et al (2017)	130	03 (2.30%)	09 (6.92%)	15 (11.53%)	27 (20.76%)	38 (29.23%)	25 (19.23%)	13 (10.0%)
Present study (2018)	48	00	02 (4.17%)	04 (8.33%)	14 (29.17%)	16 (33.33%)	08 (16.67%)	04 (8.33%)

Age distribution of CNS tumors with other studies

Sex distribution

Males were more commonly affected than females in the present study. 66.67% of cases were seen in males in comparison to 33.33% cases seen in females with a M: F ratio of 2:1. This finding was similar to other studies. Similar findings were noted by Shashidhar et al (2017)[10] with M:F :: 1.44:1.

Clinical features

In our study, the most common symptom was headache (81.25%). Shashidhar et al (2017)[10] reported headache as the most common symptom. The most likely mechanism for headache in CNS tumors could be traction on the large blood vessels and dura as well as direct compression of cranial and cervical nerve fibers by the tumor. Other common symptoms like vomiting, seizures and altered sensorium which were observed in our study were also seen in other studies of CNS tumors.

WHO grade of tumors

In our study, WHO grade I CNS tumors were the most common grade of tumors (35.42%). Sumathi et al (2016) also reported WHO grade I tumors as the most common grades in their studies. While, Jat et al (2016)[11] reported equal incidence of WHO grade I and grade IV tumors with 18 cases (37.34%) each. Since WHO grading system does not grade pituitary adenoma and metastatic carcinoma, 3 cases of pituitary adenoma and one case of metastatic carcinoma was not graded in our study.

WHO grade is based on histological features and is one component of a set of criteria used to predict response to therapy and outcome. For each tumour entity, the combination of various parameters contributes to an overall estimate of prognosis. In general, patients with WHO grade II tumours typically survive for > 5 years, and those with grade III tumours survive for 2-3 years. For patients with WHO grade IV tumours, prognosis depends heavily on whether effective treatment regimens are available. Most glioblastoma patients, and in particular elderly patients, succumb to the disease within a year. For those with other grade IV neoplasms, the outlook may be considerably better. For example, grade IV cerebellar medulloblastomas and germ cell tumours such as germinomas are rapidly fatal if left untreated, but state-of-the-art radiation and chemotherapy result in 5-year survival rates exceeding 60% and 80%, respectively[12].

WHO grades of astrocytoma

In our study, grade IV astrocytoma was the most common grade of astrocytoma comprising of 8 cases (53.33%). This was in concordance

with studies conducted by Jat et al (2016)[11] and Mehta et al (2017)[13] who also reported Grade IV astrocytoma as the most common type.

Grade I astrocytomas include various variants like pilocytic astrocytoma and subependymal giant cell astrocytoma. Grade II astrocytomas include variants like diffuse astrocytoma and pleomorphic xanthoastrocytoma. Grade III astrocytomas includes variants like anaplastic astrocytoma and anaplastic xanthoastrocytoma. Glioblastomas have been assigned grade IV.

WHO grades of meningioma

Grade I meningiomas were the most common grade of meningiomas in our study (78.57%) followed by Grade II meningioma (21.43%). These findings were also observed by Jat et al (2016)[11], and Mehta et al (2017)[13] who all reported Grade I meningiomas as the commonest type. WHO grade is the most useful morphological predictor of recurrence. Benign meningiomas have recurrence rates of about 7-25%, whereas atypical meningiomas recur in 29-52% of cases, and anaplastic meningiomas at rates of 50-94%.[14]

Even within the benign meningiomas, the presence of some atypical features (but not enough for WHO grade II designation) increases the risk of subsequent progression/recurrence over those with no atypical features at all. Malignant histological features are associated with shorter survival times of 2-5 years depending largely on the extent of resection.[15-16]

Diagnostic accuracy of radiological diagnosis with histopath ological diagnosis

Among the 48 cases diagnosed in histopathology in the present study, the diagnosis matched correctly in 46 cases in CT/MRI scan. Hence, the diagnostic accuracy of histopathological diagnosis and radiological diagnosis in our study was 95.83%. This was in concordance with studies does by Kasim et al (2013)[17], Pant et al (2015)[18] and Kumar et al (2016)[19] who reported the diagnostic accuracy of 93.18%, 96.07% and 94.54% respectively (Table 27)

One case of choroid plexus papilloma was diagnosed as acoustic schwannoma on MRI scan. The most probable reason for this error could be the location of the tumor. The tumor was located on the CP angle and it is the most common site for schwannomas. However, the exact reason could not be found.

Another case of glioblastoma was diagnosed as meningioma on MRI scan. The exact reason could not be found. But the most common explanation for this could be the tumor had well defined borders on MRI scan, while the histopathological examination revealed all the findings of glioblastoma like necrosis, nuclear atypia and mitoses.

CONCLUSION

WHO (2016) classification of CNS tumors implemented combined phenotypic- genotypic diagnostics and the increasing availability of immunohistochemical surrogates for molecular genetic alterations suggested that such challenges will be readily overcome in the near future.

Many of the genetic parameters included in the WHO (2016) classification of CNS tumors can be assessed using immunohist ochemistry or FISH, but it is recognized that some centres may not have the ability to carry out molecular analyses and that some molecular results may not be conclusive.

Though advances in molecular biology and large volumes of literature on use of ancillary techniques for better understanding of CNS tumours are on the rise, but still morphological study by histopathological techniques are still the backbone for diagnosis of these tumours.

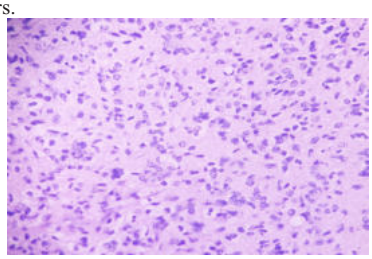

Figure 5: Anaplastic astrocytoma, grade III. Nuclear pleomorphism and increased mitotic activity (H&E X400)

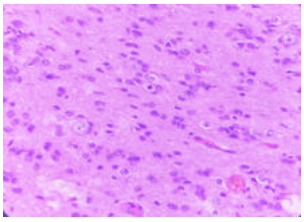

Figure 6: Glioblastoma, grade IV. Nuclear and cellular pleomorphism with atypical mitoses. (H&E X400)

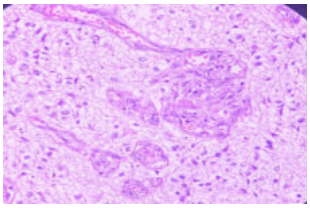

Figure 7: Glioblastoma, grade IV. Marked 'glomeruloid' microvascular proliferation.(H&E X400)

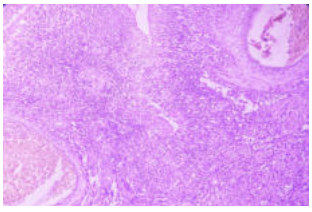

Figure 8: Glioblastoma, grade IV. Pseudopalisading necrosis. (H&E X400)

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