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Ki-67 Immuno profile in Central Nervous System Tumors

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Abstract:
The trends in cancers of the Central Nervous System are less frequently analysed due to relatively low incidence of occurrence of these tumors compared to cancers of other organs like aero-digestive tract, cervix and breast. The objective of this study was to correlate the histological grade and Ki 67 expression in various CNS neoplasms and provide a benchmark for future studies assessing data in continuum. This was a retrospective study carried out in our institution on 100 CNS neoplasms. There was positive correlation between the Ki-67 expression and histological grade showing a proportionate rise in the labelling index with the corresponding histological grade.

Key words: *CNS neoplasms, WHO grade, Ki 67, labelling index.*

I. Introduction:

The CNS tumors have always been a cause of concern to the pathologist due to the wide variety in their appearances. Grading of CNS neoplasms is fundamental for optimal prognostication and deciding on the choice of therapy. Histological grading of CNS tumors can be challenging despite criteria given by WHO more often due to limited tumor material provided. The number of mitosis is of paramount importance but can be hard to identify in the haematoxylin and eosin stained sections. Ki -67 is a novel non histone nuclear protein that is expressed in the active phases of the cell cycle and thus labelling with the monoclonal antibody against this antigen readily identifies cells that are actively proliferating.

Ii. Materials And Methods:

This study was carried out in the department of Pathology over 29 months. About 100 cases of CNS tumors were studied.All the tumors were graded according to the WHO criteria.**Exclusion criteria:**1.Reactive lesions 2.CNS infections 3.Non neoplastic cystic lesions. All the specimens were fixed in 10% neutral formalin and were subjected to histopathological examination. Sections of 3-5 micron thickness were made and routine staining with haematoxylin and eosin was done. Immunohistochemistry was done with Ki 67 antibody for selected cases that included different tumors of various grades. Immunohistochemistry was done on selected cases representing each grade of different CNS tumors, based on the peroxidise method with a standard HRP kit.

III. Results:

Table -1 shows the expression of Ki -67 in various CNS neoplasms in this study. Grade I"fig"-1, and II astrocytomas"fig"3 showed a very low expression of the antigen (<1 % and 2% respectively) "fig"-,2,4 indicating the low mitotic activity. Whereas the grade III"fig-5 and grade IV "fig"-7astrocytomas showed more than 50 % positivity."fig" – 6,8 Similarly in meningiomas as the grade increased a significant increase in the Ki 67 expression was observed with highest expression in rhabdoid meningioma -20% (grade III) "fig-13. There was very minimal expression of the antigen in grade I/II meningioma"fig"9,11 of <0.1 %."fig" ,10,12. Oligodendroglioma"fig"-15 showed a labelling index of 0.5% "fig" 16. Medulloblastoma "fig"-17 being a grade IV tumor showed an expression of 5 % "fig"-18. Other low grade tumors like ependymoma (1%),hemangioblastoma (< 1%) and schwannoma (<0.1%) showed very little expression of Ki 67 indicating very low mitotic activity and less aggressive nature of these tumors. Ki 67 labelling index was negative in ganglioglioma and in pituitary adenoma.

Table – 1 KI- 67 LABELLING INDEX OF VARIOUS CNS NEOPLASMS

S.NO	HPE Diagnosis	MIB INDEX
1.	Astrocytoma – grade - I	<1 %
2.	Astrocytoma – grade -II	2 %
3.	Astrocytoma – grade III	50-60%
4.	Astrocytoma – grade - IV	80%
5.	Gliosarcoma	60%
6.	Meningioma- grade - I	0.1%
7.	Meningioma- grade - II	8-10 %
8.	Meningioma- grade- III (Rhabdoid)	20 %
9.	Oligodendroglioma	0.5%
10.	Ganglioglioma	Negative
11.	Medulloblastoma	5 %
12.	Pituitary adenoma	Negative
13.	Hemangioblastoma	<1 %
14.	Schwannoma	< 0.1%
15.	Ependymoma	1%

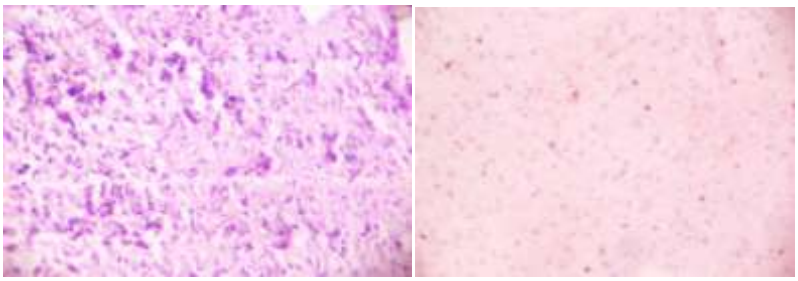

Figure 1, - Astrocytoma grade –I(H&E) ,Figure – 2 Ki-67 labelling index- <1%

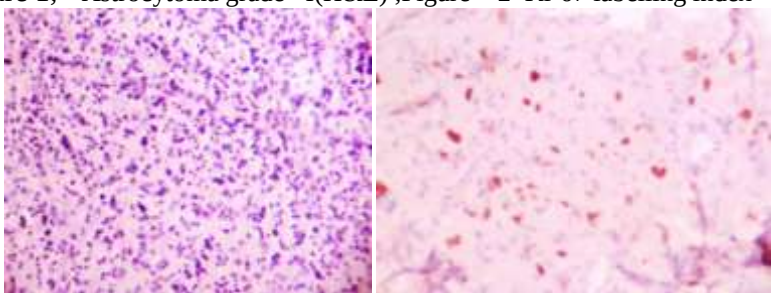

Figure 3 -Astrocytoma grade II(H& E) Figure 4 –Ki-67 labelling index - 5%

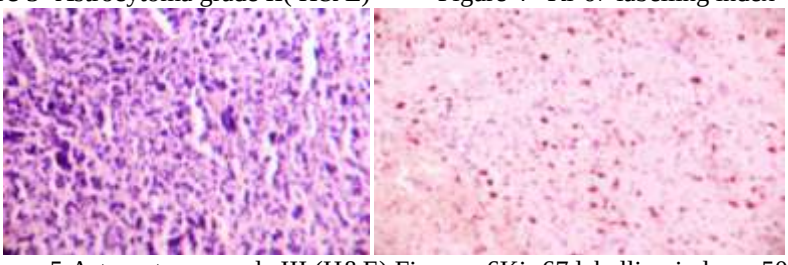

Figure -5 Astrocytoma grade III (H&E) Figure - 6Ki -67 labelling index – 50 %

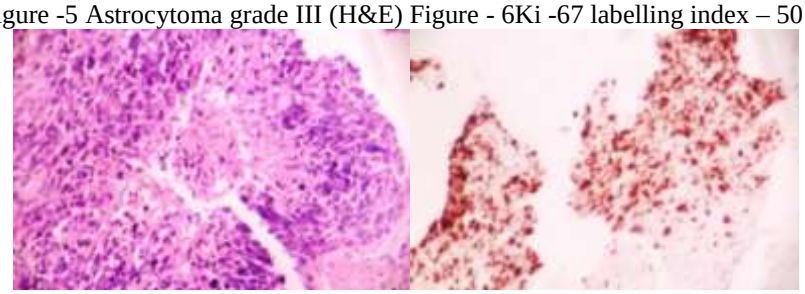

Figure – 7 Astrocytoma grade IV(H&E), Figure -8-Ki-67 labelling index - > 80 %

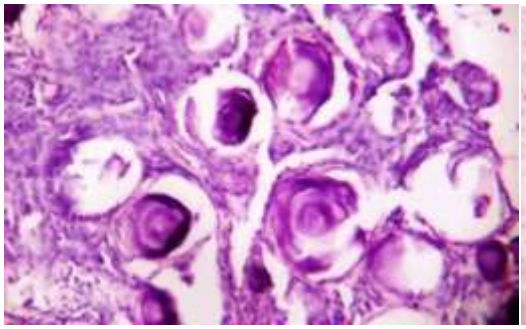
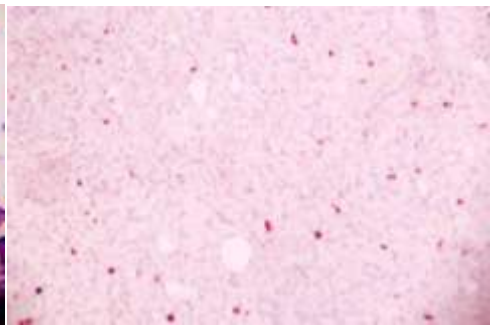

Figure -9Meningioma grade I (H&E), Figure -10 Ki -67 labelling index 1 %

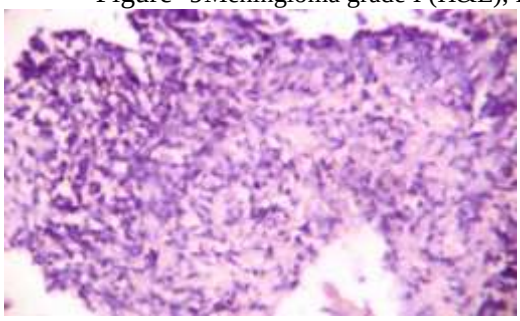
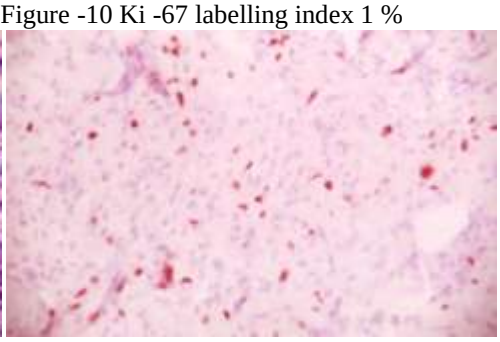

Figure 11 -Meningioma grade II(H&E) Figure- 12 Ki-67 labelling index 10 %

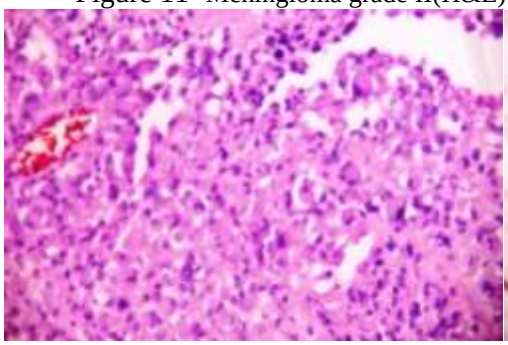
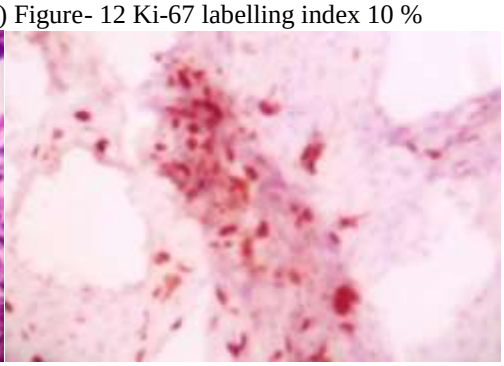

Figure 13Meningioma grade III(H&E) Figure – 14 Ki- 67 labelling index 20 %

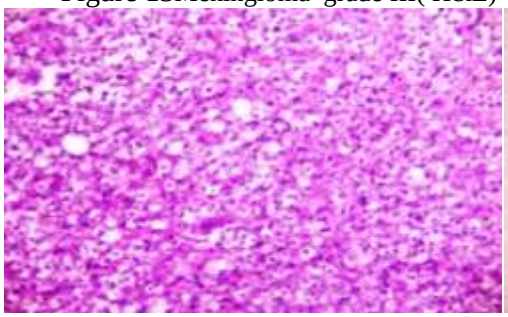
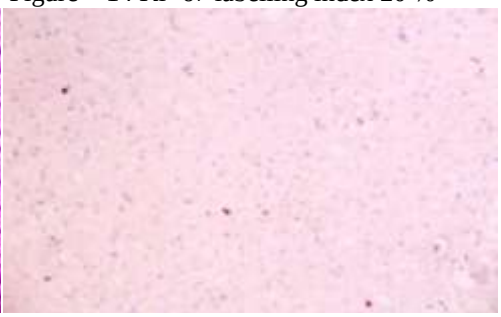

Figure 15 Oliogodendroglioma(H&E) Figure -16 Ki -67 labelling index 0.5 %

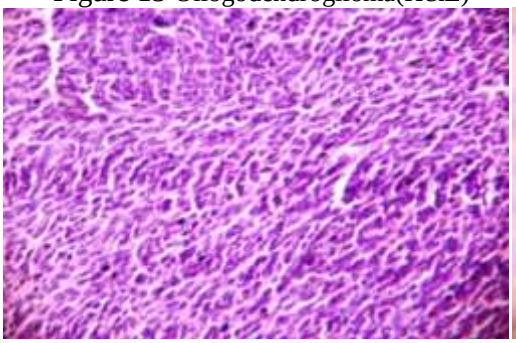
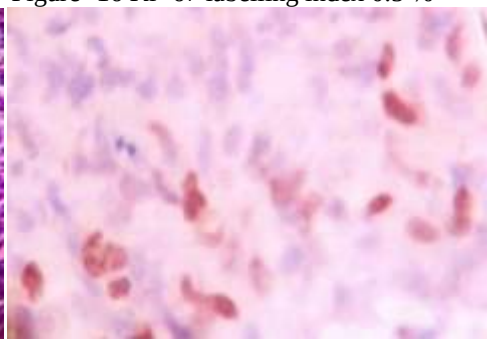

Figure -17 Medulloblastoma(H&E) Figure- 18 Ki-67 labelling index -5 %

IV. Discussion:

The central nervous system tumors are the most widely classified of all the other tumors of major systems of the body, with around 86 major tumor types apart from their variants. The CNS tumors are always a cause of concern among histopathologists due to its wide variation in the morphology and also the difficulties faced in grading these tumors accurately.

Grading of the CNS tumors in this study was done according to the WHO 2007 criteria[1]. The grading was based on the cellularity, mitotic count, microvascular proliferations, necrosis. Ki-67 is an intranuclear protein, which is present in the proliferating cells. It is present in the cells of all phases of cell cycle namely G1, S, G2 and M phase except G0 phase where the cells are in quiescent or resting stage. Thus, determination of Ki-67 is an excellent factor correlating cellular growth. MIB-1 labelling index is the number of Ki -67 labelled tumor nuclei expressed as a percentage of the total number of tumor nuclei counted. A total of atleast 1000 tumor nuclei were counted in in several areas where the positively stained nuclei were evenly distributed according to Torp SH et al[2] .All Pathologist will quickly concede , counting mitotic figures in haematoxylin and eosin sections can be extremely cumbersome and time consuming, particularly if the specimen is large or tissue preservation is poor such that it is difficult to distinguish degenerating cells from mitosis Arrie Perry

The WHO has resisted assigning any specific labelling index cutoffs in grading of individual tumor types because there is too much of interlaboratoryvariability . Wide ranging differences in staining results and counting methods making it difficult to extrapolate the results from one medical centre to another as per Johannesen et al [3], in his text has stated that keeping in mind that each tumor type is different , a useful though grossly oversimplified approach is to consider low, moderate and high proliferative indices as less than 5%, 5-10% and > 10% respectively .We evaluated the Ki 67 expression in various CNS tumors in our study.The following table shows the labelling index in astrocytomas in our study in comparison to other studies.

In our study Ki- 67 expression did not exactly correlate with any of the other studies but It should be noted that the MIB -1 labelling index did correlate with the increasing tumor grade. Gliosarcoma(grade IV astrocytoma) showed a maximum expression of Ki-67 (60 %) in our study indicating the high grade nature of the tumor with high proliferative activity.

Ki 67 expression in meningiomas also correlated well with their corresponding histological grades. The following table shows a comparison of Ki 67 labelling in meinigiomas with other studies.

Oligodendroglioma being a grade II tumor showed a 0. 5 % expression of Ki 67 which correlated with the study of Jaros et al [4] who showed an expression of 0.6 % in oligodendrogliomas. In case of medulloblastoma the expression of Ki 67 was 5 % in our study. This percentage of expression of Ki 67 was less when compared with the study of Rosalva et al [5]who showed an average expression of 27.5%. Ki 67 labelling was negative in case of ganglioglioma in our study. Wolf et al [6] in his study of 61 cases of gangliogliomas showed that in 74 % of cases the Ki 67 labelling index was < 1 %. He also showed that the labelling happened only in the astrocytic component of the tumor.

In case of pituitary adenoma the labelling was negative. According to Shrestha et al [7], Ki 67 expression in pituitary adenomas is often <1 %. Ki 67 expression was less than 1 % in case of hemangioblastoma. This value correlated with the study of Miyagami M et al [8] who showed a mean expression of 0.8 % in hemangioblastomas. According to the study of HumaArshad [9] the labelling index in case of ependymomas was 0.5 %. In our study the value was 1 %. Nerve sheath tumor usually showed a very low expression of Ki -67 and it was about 2% in the study of Saito et al [10]. In our study Ki 67 expression was < 0.1 %. Jaros et al[4] also showed a similar expression of 0.2 %.

V. Conclusion:

In this retrospective study of 100 Central Nervous system tumors that were evaluated with histochemical, histopathological and immunohistochemistry shows that Ki-67 has a great value in the histological assessment of neoplastic lesions of the CNS. It has to be used prudently in combination with histopathological features for designating the exact grade of the tumor. This can have important connotations in the field of brain tumor research particularly when analysing the geographical differences in their molecular and genetic profiles which could aid in the development of targeted individualised therapies and planning treatment protocols and strategies.

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