Histopathologic Diagnosis, Cell Cycle Parameters and Clinical Behavior of 90 Egyptian Brain Tumor Cases

A Settin, N Badr El-Din, N Ali, Abdel-Hady El, F Salem

Citation

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Abstract

This work aims at assessment of factors contributing to cell proliferation in relation to histopathologic diagnosis and clinical outcome of 90 brain tumour cases from Egypt. Cases were taken prospectively from the Neurosurgery Department of Mansoura University Hospitals, Egypt. Their median age was 46 years and their sex included 42 (46.7%) males and 48 (53.3%) females. Of these cases, 14 cases (15.6%) had an age <20 years. Brain biopsy samples were processed for histopathologic examination in addition to flow cytometeryic analysis of DNA ploidy pattern, apoptosis, p53 and Bcl2 expressions. Meningeal tumors were most frequent (37.8%) followed by astrocytic tumors (26.7%), sellar tumors (12.2%) while the neuroblastic tumors were detected in 10% of cases. Females were more affected by meningiomas and pituitary adenomas whereas males were more affected by astrocytic tumors. Older cases were affected mostly by meningeal and astrocytic tumors while the younger ones were more affected by neuroblastic tumors. Malignant tumors showed significant increased levels of mutant p53 expression, S phase of both diploid and aneuoploid cells than benign ones (P<0.05). On follow up, most of the cases affected with meningeal tumors had become symptom free while recurrence and death were mostly observed in astrocytic tumors. Significant increased expression of mutant p53 was also observed among recurrent cases (p<0.05) than cases that become free of symptoms. These results shows that cell cycle markers in addition to histopathology can help in predicting prognosis of brain tumours with a potential impact on management plan.

INTRODUCTION

The most common disease process to affect brain cells is neoplasia or tumor formation resulting in tumor of glia (glioma), meningeal cells (meningiomas), Schwann cells (schwannomas) and immune system cells (lymphomas). In children, brain tumor is the second most common form of cancer, surpassed only by leukemia. Unfortunately, many brain tumors are currently incurable. The majority of adult gliomas, for instance, is resistant to therapy and often causes death within a few years. Meningiomas and schwannomas on the other hand, are generally benign and can be treated by surgical resection. However, the removal of benign tumors from deep regions of the brain may carry considerable risk to the patient, and therefore some meningiomas or schwannomas may not be curable ([1]).

Most brain tumors occur in otherwise normal adults; that is, in people without a family history of brain tumors and without a history of exposure to an environmental toxin as smoking, or exposure to head injury, electric wires, and drugs including medications during pregnancy ([2]).

Cells reproduce by doubling their constituents, followed by division. The sum of the cell activities that is essential for their reproduction is defined as the cell cycle([3]). The cell cycle is composed of major phases. G1 phase is the time gap between the end of previous mitosis and start of DNA synthesis. It is the most variable period in the cycle. During this phase, the cell may enter in a resting state called G0 state. In some tissues that do not divide, such as nerve cells and skeletal muscles and those which rarely divide as lymphocytes, the DNA assay indicates that its bulk is in G1 period only thus showing diploid DNA content. S-phase is the most constant period of the cycle. It lasts about 7 hours. During this phase the DNA mass increases in size and amount till it reaches double the basic amount in G1 phase ending with tetraploid cell (4c). G2 phase is relatively of short period (4 hours) in which cells having double the amount of DNA (4c) become ready for division. M-phase or mitosis phase is the shortest phase of the cell cycle it takes nearly one hour. It is the final and microscopically visible stage of an underlying alteration that has occurred at molecular as well as biochemical levels. The essential features of this stage is the equal morphologic distribution of

duplicated genetic material into daughter cells over four consecutive phases known as prophase, metaphase, anaphase and telophase. It ends with the production of two new diploid cells to enter a new cycle ([4]).

Apoptosis is a complex tightly regulated, and active cellular process whereby individual cells are triggered to undergo self destruction in a manner that will neither injure neighboring cells or elicit any inflammatory reaction ([5,6]). In cases of DNA damage, apoptosis is initiated via p53 dependent pathway leading to activation of mediators such as bax and killer /DR5 ([7, 8]).

p53 gene is a general tumor suppressor gene located on the short arm of chromosome 17p31.1. It is the most common target for genetic alterations in human malignancy although little was known about the normal function of p53. It has been classified sometimes as a tumor antigen, an oncoprotein and as tumor suppressor gene ([9]). Mutant p53 gene products have a prolonged half life when compared with the wild-type protein. Over-expression of p53 protein has been identified immuno-histochemically in variety human tumors such as colorectal, lung and breast cancers ([10]).

The Bcl-2 family of proto-oncogene is a critical regulator of apoptosis, whose expression frequently becomes altered in human cancer. Bcl-2 was the first member to be identified, by virtue of its involvement in t(14;18) chromosomal translocation commonly found in ß cell non-Hodgkin's lymphoma (NHL) ([11,12]). Bcl-2 and Bcl-Xl are important in preventing cell death in glioblastoma cells ([13]).

This work aims at assessment of factors contributing to the control of cell proliferation as DNA content analysis, apoptosis in addition to p53 and Bcl-2 expression in relation to histopathologic diagnosis as clinical behaviour of brain tumors.

PATIENTS AND METHODS

This work included 90 cases presenting with an intracranial tumors detected by computerized imaging (CT and/or MRI brain) and were candidate for surgical resection. These cases were taken prospectively from the Neurosurgery Department of Mansoura University Hospitals, Egypt. Their median age was 46 years and their sex included 42 (46.7%) males and 48 (53.3%) females. Of these cases, 14 cases (15.6%) had an age <20 years. Informed consent of cases as well as an authorized approval of the University Research Council was obtained before the start of this work. Brain biopsy samples were processed for histopathology and grading in terms of diagnosis, benign or potentially malignant or malignant. In addition, cell preparation for flowcytometry (cell suspensions as well as cell fixation) was done as described for tissue samples ([14]). Flow cytometric analysis included a) cell cycle and ploidy pattern after DNA staining with propidium iodide, b) apoptosis pattern using DAKO apoptest (annexin V–FITC kit) c) p53 and Bcl-2 expression using corresponding monoclonal antibodies (Dako Corporation kits), (figures 1,2).

Figure 1

Figure 1: Histogram showing cell cycle parameters using flow cytometer software modfit showing : A) Normal diploid pattern B) Aneuploid pattern

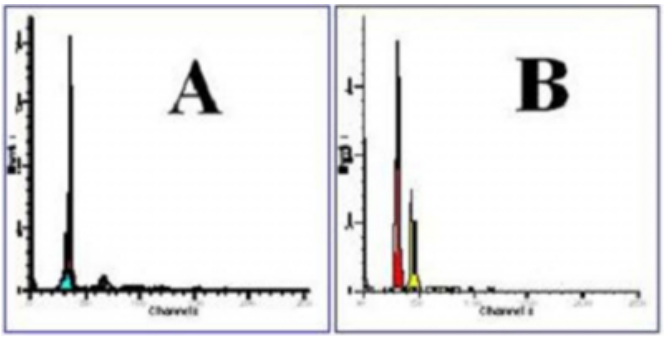
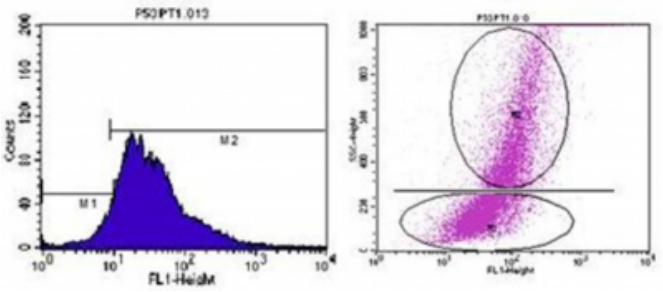


Figure 2

Figure 2: Flowcytometric analysis of p53 expression on mononuclear cells showing : (A) histogram and (B) dot plot of positively stained cells compared to negative ones.



STATISTICAL ANALYSIS

Statistical analysis was done using SPSS statistical package version 10. Descriptive data included frequencies, mean and standard deviation (SD). For comparison between groups means±SD, t-test was used with a level of $P<0.05$ is considered statistically significant

RESULTS

Cases were affected most frequently by meningeal tumors

(34/90, 37.8%) followed by astrocytic tumors (24/90, 26.7%) then sellar tumors (11/90, 12.2%) while the primitive neuroectodermal tumors and medulloblastomas were detected in 9/90 (10%) of cases (table 1). Number of female cases was slightly higher than males among all studied cases (male/female ratio 42/48). However females were affected by benign or atypical meningiomas and pituitary adenomas that are potentially benign whereas males were affected more by astrocytic tumors. The young age group <20 years constituted 15.6% of cases and were mostly affected by primitive neuroectodermal tumors and medulloblastomas (42.9%).

Figure 3

Table 1: Discriptive data of all studied brain tumor cases including histopathological diagnosis, sex and age groups

Tumor diagnosis	Total	Sex M/F	Age Groups <20Y ≥20Y
Total	**90(100%)**	**42/48**	**14(100%)** **76(100%)**
Astrocytic tumors	**24(26.7%)**	**16/8**	**4(28.6%)** **20(26.3%)**
Fibrocytic Astrocytoma	9 (9.5%)	6/3	1 8
Pilocytic astrocytoma	3 (3.2%)	2/1	2 1
Glioblastoma	7 (7.4%)	5/2	0 7
Glioma	2 (2.1%)	1/1	0 2
Mixed glioma	1(1.1%)	0/1	1 0
Oligodenderoglioma	2(2.1%)	2/0	0 2
PNET and Medulloblastoma	**9(10%)**	**3/6**	**6(42.9%)** **3(3.9%)**
Medulloblastoma	7(7.4%)	3/4	5 2
P.N.E.T.	1(1.1%)	0/1	1 0
Desmoblastic medulloblastoma	1(1.1%)	0/1	0 1
Tumor of sellar region	**11(12.2%)**	**4/7**	**0(0%)** **11(14.5%)**
Pit. Adenoma	10(10.5%)	4/6	0 10
Craniopharyngeoma	1(1.1%)	0/1	0 1
Tumor of meninges	**34(37.8%)**	**12/22**	**0(0%)** **34(44.7%)**
Benign meningioma	31(34.4%)	10/21	0 10
Atypical meningioma	1(0.01%)	0/1	0 1
Anablastic meningioma	2(2.1%)	2/0	0 2
Others	**12(13.3%)**	**7/5**	**4(28.6%)** **8(10.5%)**
Ependymoma	5(5.3%)	4/1	4 1
Large cell lymphoma	2(2.1%)	0/2	0 2
Schwannoma	2(2.1%)	0/2	0 2
Hemangiopericytoma	2(2.1%)	2/0	0 2
Choroid plexus papilloma	1(1.1%)	1/0	0 1

One year follow-up of studied cases (table 2) showed that most of the cases had become symptom free (42/90, 46.7%) that was mostly observed in the meningeal tumors group. Immediate recurrence was observed in 26/90 (32.2%) of cases that was mostly noted in astrocytic tumors. Death following operative interference for tumor resection was observed in 22/90 (24.4%) of cases, mostly noted in astrocytic tumors as well. Interestingly, among cases of meningeal tumours, 6 cases (27.27%) of benign meningiomas suffered death after surgery meanwhile both cases with anaplastic meningiomas showed cure after surgery. On the other hand, the only one case with atypical meningeoma showed recurrence after surgery.

Figure 4

Table 2: One year post-operative follow-up of cases related to histopathologic diagnosis

Tumor diagnosis	Total	Symptom free	Recurrence	Death
Total	**90(100%)**	**42(100%)**	**26(100%)**	**22(100%)**
Astrocytic tumors	**24(26.7%)**	**1(0.024%)**	**12(46.2%)**	**11(50%)**
Fibrocytic Astrocytoma	9 (9.5%)	0	7	2
Pilocytic astrocytoma	3 (3.2%)	0	0	3
Glioblastoma	7 (7.4%)	0	3	4
Glioma	2 (2.1%)	0	0	2
Mixed glioma	1(1.1%)	1	0	0
Oligodenderoglioma	2(2.1%)	0	2	0
PNET and Medulloblastoma	**9(10%)**	**2(0.047%)**	**5(19.2%)**	**2(0.090%)**
Medulloblastoma	7(7.4%)	1	5	1
P.N.E.T.	1(1.1%)	1	0	0
Desmoblastic medulloblastoma	1(1.1%)	0	0	1
Tumor of sellar region	11(12.2%)	10(23.8%)	1(0.038%)	0(0.0%)
Pituitary Adenoma	10(10.5%)	10	0	0
Craniopharyngeoma	1(1.1%)	0	1	0
Tumor of meninges	**34(37.8%)**	**24(57.1%)**	**4(15.3%)**	**6(27.3%)**
Benign meningioma	31(34.4%)	22	3	6
Atypical meningioma	1(0.01%)	0	1	0
Anablastic meningioma	2(2.1%)	2	0	0
Others	**12(13.3%)**	**5(28.6%)**	**4(15.3%)**	**3(13.6%)**
Ependymoma	5(5.3%)	2	3	0
Large cell lymphoma	2(2.1%)	1	0	1
Schwannoma	2(2.1%)	1	0	1
Hemangiopericytoma	2(2.1%)	1	1	0
Choroid plexus papilloma	1(1.1%)	0	0	1

Flowcytometric analysis of cell cycle markers (table 3) has revealed a significant increase in mutant p53 expression, S

phase cells (diploid as well as aneuploid) in astrocytic tumors than meningeal ones ($p<0.05$). Also, astrocytic tumors showed (although insignificant) higher expression of BCL-2 and lower apoptosis than meningeal ones.

Figure 5

Table 3: Flow cytometric parameters for cell cycle analysis, apoptosis, p53 and Bcl-2 expression related to pathologic grading

Cells %	Malignant Mean±SD	Benign # Mean±SD	P
Mutant p53	94.15±5.23	87.04±11.56	**0.047***
Mutant Bcl-2	80.7±9.8	81.19±16.73	0.45
Apoptotic	6.95±21.02	9.23±18.14	0.12
Necrotic	0.51±0.41	11.4±20.2	**0.04***
G0G1	33.68±7.54	27.47±4.27	0.15
G2M	63.70±9.17	56.27±11.13	0.24
S_diploid	22.42±15.80	6.39±11.98	**0.026***
G2/G1	1.93±0.33	2.04±0.14	0.42
S_aneuploid	25.54±5.07	2.71±5.90	**0.038***
DNA index	1.04±.08	1.14±0.15	0.13

*P<0.05 i.e statistically significant using t-test.

anaplastic and atypical tumours were excluded from analysis being potentially malignant

Considering tumour recurrence is a potential measure of tumour aggressiveness, we have compared flow cytometric parameters of cases of recurrent tumour vs cases free of symptoms in the first year after surgery (table 4). Recurrent tumours showed a significant increased mutant p53 ($p<0.05$), with also nonsignificant increased expression of mutant Bcl-2, G0G1 phase diploid cells, S phase aneuploid cells and lower apoptosis than cases with symptom free after surgery.

Figure 6

Table 4: Flowcytometric parameters for cell cycle analysis, apoptosis, p53 and Bcl-2 expression related to immediate prognosis of brain tumor after surgery in the studied subjects

Cell %	Symptom free Mean±SD	Recurrence Mean±SD	P
Mutant p53	86.95±7.84	93.89±5.95	**0.019***
Mutant Bcl-2	80.6±16.55	85.3±5.36	0.984
Apoptotic	10.41±20.75	0.53±0.47	0.058
Necrotic	12.4±21.4	0.61±0.39	**0.013***
G0G1	25.75±13.73	32.29±2.95	0.104
G2M	63.66±23.94	60.77±14.07	0.588
S_diploid	13.15±16.40	13.96±14.07	0.797
G2/G1	4.7169±8.22	1.91±0.51	0.197
S_aneuploid	8.73±0.25	16.81±30.06	0.779
DNA index	1.09±23.94	1.08±0.15	0.914

*P<0.05 i.e statistically significant using t-test.

DISCUSSION

Tumors of central nervous system (CNS) have special features that make them different from other neoplasm in the body. Firstly the distinction between benign versus malignant tumors is less evident. Secondly, irrespective of histological classification they can be highly malignant depending on their anatomical location. Thirdly they rarely metastasize outside the CNS although they often, infiltrate into the surrounding brain parenchyma ([15]).

It has been reported that about 50% the primary neoplasms were gliomas and 50% of these gliomas were mostly malignant glioblastomas whereas meningiomas were the most common type of the non gliomatous primary brain tumors followed by schwannomas which make up 20% and 10% of brain tumor respectively. Meningiomas are tumors in arachnoids cells which represent up to one fifth of all intracranial tumors and up to a quarter of spinal neoplasias. Although meningiomas have classically been considered to be benign tumors, it has also been well-established that they show a heterogeneous clinical outcome ([15,16]).

In this study, about one third of brain tumour cases were affected by meningeal tumors followed by astrocytic tumors (one forth) while both sellar tumors and primitive neuroectodermal tumors were detected in one tenth of cases. Although, most of meningeal tumours were diagnosed as benign by histopathology; yet 6 have died after surgery.

Most authors have reported an incidence rates of brain tumours consistently increasing with age but then decreasing in the very old patients ([17]). In agreement with that observation, half of the studied cases were in the middle age group (20-50 years) followed by the older age group >50 years while the younger age group <20 years showed the least frequency. Moreover, young age group (<20 years) was mostly affected by primitive neuro-ectodermal tumous and medulloblastomas while the older groups were mostly affected by meningeal and astrocytic tumors. This is consistent with what was previously reported that medulloblastoma is the most common malignant brain tumor of childhood, accounting for approximately 20 % of all primary tumors of central nervous system among children less than 19 years old ([18], [19]).

In the current study, number of female cases was slightly higher than males. However, female affection was mostly observed in benign and atypical meningiomas and pituitary adenomas that are potentially benign whereas male affection was observed in astrocytic tumors that are potentially malignant. This confirms what have been reported previously that the incidence of brain tumors although was more common in males than females but with higher frequency of meningiomas and nerve sheath tumor in women than in men ([20], [21]).

Authors concluded that in patients with high grade malignant brain glioma such as glioblastoma, recurrence occurs between 6 and 12 months and for anaplastic astrocytoma within 18 - 36 months where survival is generally related to tumor histopathology anatomic location and age of patient as younger glioma patients survive longer ([15],[22]). Likewise, currently studied glioblastoma and glioma cases showed bad prognosis after surgery in the form of death or rapid recurrence. On the other hand, the single case of mixed glioma affecting a female infant 6 months of age was totally resected with apparent relief of symptoms after surgery. Fibrocytic astrocytoma showed also bad prognosis of recurrence or death after surgery whereas pilocytic astrocytoma -although described as a low grade tumor- showed bad prognosis as well.

The p53 tumor suppressor gene is mutated in 60% of human tumors and its product acts as a suppressor of cell division. The role of p53 in suppressing tumorgenesis may be to rescue the cell organism from the mutagenic effects of DNA damage so the loss of p53 function accelerates the process of tumorigenesis and alters the response of cells to agents that damage DNA ([20],[23],[24]). Abnormalities of the p53 tumors suppressor gene are found in significant proportion of astrocytic brain tumors ([25]). In the present work the % of mutant p53 cells was significantly higher in malignant cases than benign cases and was higher in astrocytic tumors in comparison to meningioma cases.

DNA ploidy and cell cycle has been simultaneously assessed in a large series of meningioma tumors to explore the prognostic value of DNA ploidy status and the proliferative rate of tumor cells. Results showed that meningioma tumors displayed a relatively low incidence of DNA aneuploidy (14%), with a low proliferative rate (lower S-phase cells) ([16]). Analysis of DNA cycle parameters of our studied cases using flow cytometry showed also a significant lower level of S phase cells both diploid and aneuploid ones in benign meningiomas than that of astrocytic tumors. These meningioma cells showed also significant higher level of necrosis with high level (although non significant) of apoptosis as well. Defects in the apoptosis inducing pathways can eventually lead to expansion of a population of neoplastic cells ([26]).

Bcl-2 is the first identified survival gene involved in the control of apoptosis. The Bcl-2 family of proto-oncogenes includes members that both inhibit and induce apoptosis ([27]). Also Bcl-2 is known to protect cells from a variety of apoptotic stimuli including oxidative stress ([28]). Studies have shown a correlation between high levels of Bcl-2 expression and the severity of malignancy of human tumors. Down regulation of Bcl-2 and Bcl-xl protein may be a potential target to enhance cell death in glioblastomas ([29],[30]).

It has been stated that the survival of patients with brain gliomas depends on well-established prognostic factors that include over expression of p53 protein through over trapping mechanisms, independent of actual p53 mutations ([31]). In the current study, comparing flow cytometric parameters in cases free of symptoms after surgery with those having tumor recurrence showed a significant increased cells expressing mutant p53 among recurrent cases. In addition recurrent cases have shown also an increased expression of mutant Bcl-2, diploid cell in G0G1 phase, aneuploid S phase cells with less amount of apoptosis and necrosis than cases with symptom free after surgery.

We can come to the conclusion that flow cytometric analysis of cell cycle, apoptosis and p53 and Bcl-2 expression in addition to histopathology of brain tumor biopsies can be

considered important markers for prognosis that may help in modification of therapy and follow up of these cases.

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Author Information

A. Settin

N. Badr El-Din

N. Ali

Abdel-Hady El

FK Salem