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Primary Brain Tumors in A Sample of Adult Iraqi Patients (Clinicopathological Study)

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Abstract

Background Primary brain tumors are a diverse group of neoplasms. More than 120 histological types of these tumors have been classified by the World Health Organization (WHO). Brain tumors exhibit different behaviors according to age, histological type and location. In Iraq, few epidemiologic reports have highlighted the national and regional epidemiologic data regarding primary central nervous system (CNS) tumors.

Objective To identify the frequency of different histopathological types of primary brain tumors in samples of Iraqi patients, and to study the association with some clinicopathological parameters like age, gender, location and grade.

Methods A cross-sectional study including analysis of (200) patients who were presented with primary brain tumors. The samples are collected from Neurosurgery Teaching Hospital, Ghazi Al-Hariri Surgical Specialties Hospital and privet lab from January 2021 to January 2022.

Results The mean age was 42.94 years, ranging from (18 to 76) years, females were more than males as (55% and 45% respectively). Regarding anatomical location; supratentorial was 71% and infratentorial was 29%. With regard to histological types; diffuse glioma (43%) (from which glioblastoma most common subtype 59.3%) followed by meningioma (38%) (from which meningothelial meningioma represent 66.4). However, the ependymal tumors were only (3.5%). There was significant association between histological type and age (P = 0.005), and between histological type and grade (P = 0.001). However, there was no significant association between histological type and sex (P = 0.701).

Conclusion Diffuse glioma was the most common type that occur commonly in female and majority of cases situated in supratentorial region, also there was significant association between histological type with age and grade.

Keywords Adult tumors, glioma, histopathology, meningioma, primary brain tumor

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List of abbreviations: CNS = Central nervous system, IDH = Isocitrate dehydrogenase, NOS = Not otherwise specified, WHO = World health organization

Introduction

Primary brain tumors are diverse group of neoplasms. More than 120 histological types of these tumors have been classified by the World Health Organization (WHO). Unlike other tumors, they are not staged and WHO have assigned a Grade (I through IV) to predict their outcome [(1)]. Conventionally, brain tumors are classified according to the cells of origin or the sites of the origin such as neuroepithelial origin (including astrocytic tumors, oligodendrocytic tumors, ependymal tumors, choroid plexus tumors, neuronal and mixed neuronal-glial

tumors, pineal tumors, and embryonal tumors), tumors of cranial nerves, tumors of the meninges, lymphomas and hematopoietic neoplasms, germ cell tumors, tumors of the seller region, and metastases. A recent update in the WHO classification of brain tumor (2016) introduced a greater reliance on molecular markers [2,3].

CNS tumors show a bimodal age distribution with one peak in children and another peak in 45-70 years of age. The tumors are more common in males, with the exception of meningiomas, which are more frequently seen in females [4]. In Iraq, brain tumors rank fourth among the ten death leading cancers, which are registered during 2020, it accounts 6.21% of the total and 4.9% incidence rate/100,000 population [5].

With the introduction of newer diagnostic modalities, including molecular studies, the diagnostic accuracy has increased tremendously, since the exact histopathological diagnosis of brain tumors has played vital part in the diagnosis, management, and follow-up [6].

CNS tumors exhibit different behaviors according to age, histology, and location [7]. The exact etiology of the brain tumor remains unknown; however, genetic alterations, developmental abnormalities, and environmental factors have been reported to play a vital role in the etiopathogenesis of these tumors. The histopathological examinations are crucial for a definitive diagnosis and as a predictor of prognosis [8,9].

CNS tumor grading

CNS tumor grading has for many decades differed from the grading of other, non-CNS neoplasms, since brain and spinal cord tumors have had grades applied across different entities [9]. As discussed below, the 5th edition of WHO CNS tumors classification (WHO CNS5) has moved CNS tumor grading closer to how grading is done for non-CNS neoplasms but has retained some key aspects of traditional CNS tumor grading because of how embedded such grading has been in neuro-oncology practice. Two specific aspects of CNS tumor grading have changed for WHO CNS5: Arabic numerals are employed (rather than Roman numerals) and neoplasms are graded within types (rather than across different tumor types) [10]. Nonetheless, because CNS tumor grading still differs from other tumor grading systems, WHO CNS5 endorses use of the term “CNS WHO grade” when assigning grade [11], as showed in figure [1].

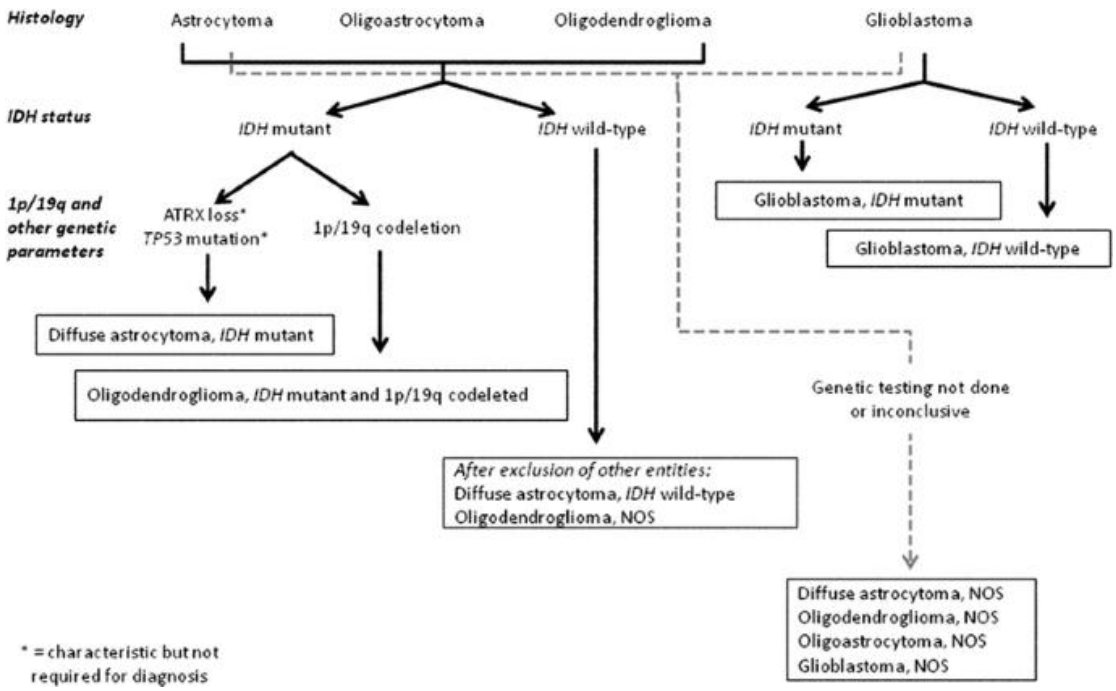

Figure 1. Diffuse gliomas "the most common type": from histology, isocitrate dehydrogenase (IDH) status, and other genetic parameters to WHO diagnosis [10,11]

The study objectives were:

1. To identify the frequency of different histopathological types of primary brain tumors in sample of Iraqi patients.
2. To study the association of these primary tumors with some clinicopathological parameters like age, sex, location, and grade.

Methods

Study design and duration

A cross-sectional study including analysis of 200 patients presenting with primary brain tumors, the samples were collected from Neurosurgery Teaching Hospital, Ghazi Al-Hariri Surgical Specialties Hospital and privet laboratory. The collection period was from January 2021 to January 2022 while the research period was from March 2022 to March 2023. The study targeted sample of adult patients who presented with primary brain tumors; not all the patients admitted during 2021, and the histopathological samples were collected postoperatively and the final diagnosis depended on both radiological and histopathological reports.

The collected data

Patient's age, sex, tumor location, histopathological type and grade were obtained from each patient's histopathological report. Collected samples were histopathological reports, as well as slides and formalin fixed paraffin embedded blocks.

From formalin fixed paraffin embedded blocks (4 µm thick) sections were cut and mounted over a glass slide and stained with routine Hematoxylin and Eosin (H&E) stains the diagnoses were revised by senior pathologist (supervisor of this study) and compare with previous results.

All the primary brain tumors were divided into the eleven-category diffuse glioma, other astrocytic tumors, ependymomas, meningeal tumors, embryonal tumors, tumors of seller region, neuronal, choroid plexus tumors, mesenchymal tumors, tumors of the cranial and paraspinal nerves, primary lymphomas. In addition to histology, molecular parameters

were also included in the 2016 WHO classification of CNS tumors [10]. Since the molecular testing and cytogenetic studies were not available in our institution the diagnosis was classified as tumors not otherwise specified (NOS).

Inclusion criteria

- Primary brain tumors.
- Patients age >18 years.

Exclusion criteria

- Metastatic tumors
- Pediatric age group
- Pituitary tumors

Tissue re-sectioning and staining was done by routine H&E stain, and image capture was done. Each H&E-stained slide was initially examined using a light microscope (Leica, Germany) at 10x and 40x magnifications to look for histopathological features indicative of the disease, and then microscopic sections photomicrograph were taken with Realme 7 pro camera [64 MP, f/1.8, 26 mm (wide), 1/1.73", 0.8µm, PDAF]. The images were captured at a resolution of 5984 × 3366 pixels.

Ethical and official approval

- Data were exclusively used for the purpose of this study.
- Approval of Scientific council of histopathology/Iraqi board of medical specialization.

Statistical analysis

Statistical analysis using the Statistical Package for Social Science (SPSS 23). Descriptive statistics (frequencies, percentage, means and standard deviations) were applied to all demographic, histopathological data. Chi square test for analytic data, p value of less than 0.05 was considered significant.

Results

The total sample of present study was 200 patients, the mean age was 42.94±15.04 years with 18 years as a minimum age and 76 years as a maximum age. Regarding sex distribution, it has been found that females are more predominant than males as (55% and 45% respectively).

The current study shows wide distribution of primary brain tumors. Concerning their location, the highest frequency has been found in supratentorial (71%). Among which are; frontal, parietal and cerebral convexities (21%, 13% and 9 respectively) and 29% for infratentorial lesions as shown in table (1).

Regarding to grading of tumor, the result showed the highest prevalence is in grade 1 and grade 4 were (43% and 27% respectively) while grade 2 and grade 3 were (13.5% and 15% respectively) with one cases of high grade as shown in table (2).

The result of present study shows the most common subtypes among patients with diffuse glioma are glioblastoma (NOS) and anaplastic astrocytoma (NOS) (59.3% and 25.4% respectively), while the patients with ependymal tumors, the highest frequency are with anaplastic ependymoma (40%) and ependymoma (30%). Whereas patients with meningioma, the meningothelial meningioma are the most common subtypes (66.4%) as shown in table (3).

The result of study shows that there are statically significant association between histological types and age category (P = 0.005), diffuse gliomas are more common in age lower than 45 years old, while meningioma most common in older age (>45 years) on contrary all cases of ependymoma in age lower than 45 years old as shown in table (4).

Table 1. Distribution of study sample according to anatomical location [The classification below is according to WHO classification 2016 and 2021] [11]

Location	Frequency	Percent
Supratentorial	**142**	**71.0**
Anterior fossa	1	0.5
Attached to falx cerebri	1	0.5
Basal ganglia	1	0.5
Cavernous sinus	1	0.5
Cerebral convexities	18	9.0
Frontal lobe	43	21.0
Interhemispheric	1	0.5
Intracranial	3	1.5
Intraventricular mass	7	3.5
Occipital mass	4	2.0
Parasagittal	6	3.0
Parietal lobe	26	13.0
Suprasellar	7	3.5
Temporal lobe	18	9.0
Thalamic	3	1.5
Third ventricle	2	1.0
Infratentorial	**58**	**29.0**
Base of skull	24	12.0
Cerebellum	23	11.5
Cerebellopontine angle	6	3.0
Fourth ventricular	2	1.0
Pons	1	0.5
Posterior fossa	2	1.0
Total	200	100

Table 2. Distribution of study sample according to grading

GRADE	Frequency	Percent
Grade I	86	43.0
Grade II	27	13.5
Grade III	30	15.0
Grade IV	55	27.5
High grade	2	1.0
Total	200	100

Table 3. Distribution of study sample according to histological types and subtypes [the classification is according to WHO classification 2016 and 2021] [11]

Histological types	Sub types	No. (%)
Diffuse glioma	Anaplastic astrocytoma (NOS)	22 (25.6)
	Anaplastic oligodendroglioma (NOS)	3 (3.5)
	Diffuse astrocytoma	3 (3.5)
	Diffuse astrocytoma (NOS)	2 (2.3)
	Gemistocystic astrocytoma	1 (1.2)
	Glioblastoma (NOS)	51 (59.3)
	Oligodendroglioma (NOS)	4 (4.7)
Embryonal tumors	Medulloblastoma (NOS)	2 (66.7%)
	Nodular desmoplastic medulloblastoma	1 (33.3%)
Ependymal tumor	Anaplastic ependymoma	4 (51.1%)
	Ependymoma	3 (48.9%)
Meningioma	Anaplastic meningioma	1 (1.3%)
	Meningiothelial meningioma	51 (66.4%)
	Atypical meningioma	10 (13.0%)
	Clear cell meningioma	1 (1.3%)
	Fibroblastic meningioma	5 (6.5%)
	Lymphoplasmacytic meningioma	1 (1.3%)
	Psammomatous variant	1 (1.3%)
	Secretory	1 (1.3%)
	Transitional	5 (6.5%)
Choroid plexus tumors	Choroid plexus carcinoma	1 (50.0%)
	Choroid plexus papilloma	1 (50.0%)
Mesenchymal tumors	Hemangiomablastoma	2 (100%)
Pineal parenchymal tumor	Papillary tumore of pineal region	1 (100%)
Other astrocytic tumor	Pilocystic astrocytoma	5 (100%)
Cranial and paraspinal	Shwannoma	6 (100%)
Neuronal tumors	Central neurocytoma	1 (100%)
Tumors of sellar region	Craniopharyngioma	5 (100%)
Lymphoma	Diffuse large B cell	2 (100%)

Table 4. Age distribution of the study according to histological types

Histological type	18-45 years No. (%)	>45 year No. (%)	Total No. (%)
Choroid plexus tumors	1 (0.9%)	1 (1.1%)	2 (1.0%)
Cranial and paraspinal ne	4 (3.7%)	2 (2.2%)	6 (3.0%)
Diffuse glioma	51 (46.8%)	35 (38.5%)	86 (43.0%)
Embryonal tumors	3 (2.6)	0 (0.0%)	3 (1.5)
Ependymoma	7(6.4)	0 (0.0%)	7 (3.5%)
Lymphoma	0 (0%)	5 (5.5%)	5 (2.5%)
Meningioma	32 (29.4%)	45 (49.5%)	77 (38.5%)
Mesenchymal tumors	1 (0.9%)	1 (1.1%)	2 (1.0%)
Neuronal tumors	1 (0.9%)	0 (0.0%)	1 (0.5%)
Other astrocytic tumor	4 (3.7%)	1 (1.1%)	5 (2.5%)
Pineal parenchymal tumor	1 (0.9%)	0 (0.0%)	1 (0.5%)
Tumors of seller region	4 (3.7%)	1 (1.1%)	5 (2.5%)
Total	109 (100%)	91 (100%)	200 (100%)
Pearson Chi-Square P value = 0.005			

Also, there are statically significant association between histological types and grading (P = 0.001), among diffuse glioma most common grade was grade IV, while grade I was the most common in meningioma and grade III in ependymoma as shown in table (5).

Regarding the histological subtypes and sex among diffuse glioma, glioblastoma is more common in females, while anaplastic astrocytoma is more common in males, however in meningioma most of the subtypes are more common in females as shown in table (6).

Table 5. Grade distribution of the study according to histological types

Histological type	Grade I	Grade II	Grade III	Grade IV	High grade	Total
Choroid plexus tumors	1	0	1	0	0	2
Cranial and paraspinal ne	6	0	0	0	0	6
Diffuse glioma	1	10	24	51	0	86
Embryonal tumors	0	0	0	3	0	3
Ependymoma	0	3	4	0	0	7
Lymphoma	0	0	0	0	5	5
Meningioma	63	12	1	1	0	77
Mesenchymal tumors	2	0	0	0	0	2
Neuronal tumors	0	1	0	0	0	1
Other astrocytic tumor	5	0	0	0	0	5
Pineal parenchymal tumor	0	1	0	0	0	1
Tumors of sellar region	5	0	0	0	0	5
Total	86	27	30	55	2	200
Pearson Chi-Square P value = 0.001						

Table (6): Sex distribution of the study according to histological types

Subtypes	Male	Female	Total
Anaplastic astrocytoma (NOS)	13	10	23
Anaplastic ependymoma	1	3	4
Anaplastic meningioma	0	1	1
Anaplastic oligodendroglioma (NOS)	1	2	3
Atypical meningioma	5	5	10
Central neurocytoma	0	1	1
Choroid plexus carcinoma	0	1	1
Choroid plexus papilloma	1	0	1
Clear cell meningioma	0	1	1
Craniopharyngioma	3	2	5
Diffuse astrocytoma (NOS)	3	2	5
Diffuse large b cell	0	2	2
Ependymoma	2	1	3
Fibroblastic meningioma	4	1	5
Gemistocystic astrocytoma	1	0	1
Glioblastoma (NOS)	20	31	51
Hemangioma blastoma	2	0	2
Lymphoplasmacytic	0	1	1
Medulloblastoma (NOS)	0	2	2
Meningothelial	21	30	51
Nodular desmoplastic medulloblastoma	1	0	1
Non-Hodgkin's	1	2	3
Oligodendroglioma (NOS)	2	2	4
Papillary tumor of pineal region	0	1	1
Pilocystic astrocytoma	2	3	5
Psammomatous variant meningioma	0	1	1
Secretory meningioma	0	1	1
Schwannoma	4	2	6
Transitional meningioma	2	3	5
Total	90	110	200
Pearson Chi-Square P value = 0.383			

Discussion

Primary brain tumors are heterogeneous group of neoplasm with large variations; they are classified according to histopathologic criteria and immunohistochemical data into different histological subtypes, these variations involve also the interpretation criteria, diagnostic modalities, therapeutic approaches and registries practiced in different countries [(12)]. Due to the high mortality seen in CNS tumors, they form the most challenging group of tumors for oncologists [(13)].

The present study recruited 200 patients, the mean age was 42.94±15.04 years ranged from (18-76) years, which agrees with Iraqi study by Saeed et al. in 2019 [(14)] and Saudi Arabian study by Mohammed et al. in 2019 [(15)]. The mean age in both studies was 43 years and 42.9 years respectively, while it was higher than the mean age of the studied sample of Al-Hashimi and Alkhateeb study in 2020 [(16)], which was 37 years. This variation in the age distribution could be explained due to difference in sample size and sampling technique among the

studies. In addition, this difference is the hallmark of CNS tumors and considered as a prognostic factor. In general, older patients (i.e. ≥45 years) showed worse prognosis than those aged under 45 years [17]. The Central Brain Tumor Registry of the United States assess in 2019 the contemporary burden of malignant and nonmalignant brain and other CNS tumors by histology, anatomic site, age, sex, and race/ethnicity, reported that malignant brain tumors incidence rates declined by 0.8% annually from 2008 to 2017 for all ages combined but increased among children and adolescents [18].

The current study has shown a female predominance, more than half of cases were females, with male to female ratio 1:1.2, which goes in agreement with (Kanthikar et al. 2017) [19], and (Thambi et al. 2017) in India [20], and also with CBTRUS Central Brain Tumor Registry of the United States" report [18], which reported a female predominance in the presentation of primary brain tumors, but differs from Mohammed et al. (2019) [15] and Thakur et al. studies who found a different results and reported a male predominance [21]. This variation can be attributed to the differences in geographical distribution and methods of registration. Studies have reported that males are more likely to develop brain tumors than females at all ages, including in childhood brain tumors. That is why it cannot be explained solely by the effects of sex hormones, there must be potential "sex-specific genetic risk factors" and "specific sex biology", which have been reported in a specific manner.

According to tumor location, the present study found that supratentorial region was the most common site of involvement (71%) while the infratentorial represent only (29%). Among the supratentorial tumors, majority of the lesions were found in frontal lobe, Parietal lobe, cerebral convexities and temporal lobe respectively, while among infratentorial lesions the base of skull and cerebellum were the most common site of involvement. These findings are in agreement with Tamimi et al. [22] study who found the same distribution of primary brain tumors when they investigate the trends of brain tumors in Jordan, the same findings were reported by Hamdani study in India [2].

Regarding histological type, the present study has found that diffuse glioma is the most common type followed by meningioma followed by other histological types. This is in line with Magwesela et al. study in 2022 [23], Hewedi et al. in 2018 [24] in Egypt, and Ekpene et al. in 2018 [25] who have reported a similar result when they investigated primary brain tumors in different samples worldwide. However, Kanthikar et al. and Thambi et al. [19,20] had reported different results, their studies have revealed a predominance of meningioma over other primary CNS tumors.

Diffuse gliomas are the most common malignant primary brain tumors in adults. Updated advances in molecular and genetic biology had improved the understanding of glioma pathogenesis, in addition to many significant genetic alterations that had been described to aid the diagnosis [26].

Among diffuse glioma, the present study has revealed that glioblastoma is the most common type followed by anaplastic astrocytoma, percentage of glioblastoma is higher than other studies by Hamdani et al. [2], Thakur as et al. [23] in India and Hewedi et al. [24], who have revealed a lower percentage than in current study. Mean age of glioblastoma is (46 years), which was lower than Thambi et al. (2017) [20] also two cases had been got at the age of 18 and 19 years old, this difference may be due to genetic factors, inclusion and exclusion criteria or more accurately in Iraq due to environmental exposure like radiation, toxins or other chemical material.

The second most common CNS tumor is meningioma among which, meningothelial meningioma, which is the most common 66.4% similar to Hussein and Abbas (2021) in Iraq [27], Solanke et al. 2020 [28], followed by atypical meningioma, transitional and fibroblastic while Thambi (2017) [20] and, Hewedi et al. (2018) [24] in Egypt have found that transitional meningioma was the commonest subtype. It has been stated that categorizing these tumors into histological subtypes is generally of little significance in grade I meningiomas. However,

recognition of special variants and atypical meningiomas is of paramount importance due to their more aggressive and recurrent nature.

Meningioma in the present study is predominantly found in females, which agrees with most of other studies, Sen et al. (2022) in India [29], Motah et al 2021 [30], Joshi et al. (2014) [31]. This can be attributed to the association of disease risk with the presence of sex hormone receptors in meningiomas, which has been observed but still controversial, However, a positive association between the use of hormone replacement therapy and the diagnosis of meningioma in women is also hypothesized, Further studies are needed to confirm a definitive underlying cause for the relatively higher incidence of meningioma in female patients [32].

The present study finds that, according to WHO grading system 2016, grade I is the most common grade among the studied sample is followed by grade IV. The WHO 2016 classification presents the highest number of modifications since the first initial WHO classification in 1979 and it forces all pathologists and professionals in the field of neuro-oncology to understand the new concepts, as the field of brain tumors has shown a dramatic increase in knowledge over the last years [26]. An Iranian study by Salehpour et al. (2019) finds according to WHO Grading of brain tumors that, the majority of patients classified as Grade I and Grade IV, and the least proportion were in Grade II, Grade III respectively [33]. It has been found that the proposed three-level grading system for WHO grade II and III gliomas and glioblastoma is correlated with the degree of histological dedifferentiation and is proved accurate in terms of survival upon both internal and external validation. While current findings differ from Armstrong et al study, who study brain tumors according to this classification and find that, high grade tumors are the most common types followed by other grades [34].

Among meningioma, grade I is the most common grade followed by grade II same as Ghanghoria et al. 2014 [34] who find that WHO grade I is the commonest.

A significant association was found between histological types and subtypes with age category where the glioblastoma (NOS) and meningothelial tumors subtypes are presented mainly in the age group more than 45 years. The above-mentioned results, are different from Thambi et al. [20] study who reported that diffuse gliomas were more common in males and a higher mean age of glioblastoma and meningothelial tumors than what is reported in the current study. While Louis et al. (2022) [35] agree with the findings of the current study in terms of age and sex.

The present study finds a statically significant association between histological types and subtypes with grading, diffuse glioma and meningioma were the most common types, which were presented in grade I tumors followed by atypical meningioma (grade II), this is disagree with Hewedi et al. study [24] in Egypt who has found that transitional meningioma is the most common subtype among primary brain tumors of the studied sample.

It is worth to mention that diagnosis of a suspected brain tumor is depends mainly on an appropriate brain imaging and histopathology, which relies recently on molecular features and histology, to reach an "integrated diagnosis", and better captures treatment and prognosis.

In conclusion, primary brain tumors had been detected more in female patients, with supratentorial lesions were the most common site of involvement. The most common histopathological types were diffuse glioma (from which glioblastoma was the most common subtype), and meningioma was the second most common type followed by ependymal tumors. A statistically significant association was found between histological types/subtypes with age of patients and grade of the tumor. These facts are the corner stone for advances in detecting, updating grading system and the use of immunohistochemistry and molecular pathology in this field. This study established a baseline of brain tumor pattern on the basis of histopathological experience at a tertiary care hospital in Baghdad, Iraq. Additionally, it provides a platform to workup for future population

targeted studies using cytogenetic, molecular study and "next-generation sequencing".

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Author contribution
Dr. Hilal: data collection, results and discussion.
Dr. Latif: literature review, editing.

Conflict of interest
None.

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