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Research Article
Central Nervous System

Histologic subtypes of Meningiomas: Review and variation in an African population

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Background: Meningiomas are considered to be the commonest neoplasm of the central nervous system and are also the most studied meningeal tumours. According to the WHO 2020 classification of meningiomas, fifteen subtypes have been grouped into grades 1, 2 and 3. The WHO grade 1 meningiomas are generally grouped as benign while the WHO grade 2 and 3 tumours are grouped as malignant. This study aims to show the variation of these subtypes with the age, gender and location in an African population. **Materials and Methods:** A 10-year retrospective review of all histologically diagnosed Meningiomas from 1st January 2010 to 31st December 2019 is presented. The distribution of the tumour in relation to the age, sex and location was assessed in this study. **Results:** The three WHO grades of meningioma were assessed in this study. The M:F ratio was 1:1.4 and peak age incidence was seen in individuals 41 – 50 years (SD ± 16.54). The majority of the cases were WHO grade 1 (86.1%) while WHO grades 2 and 3 tumours were 8% and 5.9% respectively. A slight variation in the common subtypes in males and females was observed. The fibroblastic variant was the overall commonest subtype (27.1%). **Conclusion:** The diversity of the subtypes of meningiomas of meningioma calls for strict classification protocols for standardisation of patients' grouping and potentially, management. Tumour genetics of the subtypes can be explored for the potential management of complicated cases.

Keywords: Central Nervous System, Meningioma, African population

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Introduction

Meningiomas are the commonest tumours of the central nervous system (CNS) and account for 24% of intracranial tumours in Nigeria[1]. In Nigeria, various studies have been done with varying prevalence rates. A study from Ibadan reported a prevalence rate of 11.4% among CNS tumours with a slight male preponderance[2]. However, an independent study done by Soyemi et al[3] in Lagos Nigeria showed that meningiomas ranked as the second most commonly diagnosed intracranial tumour after gliomas. A study conducted in Enugu, South East Nigeria by Ndubuisi et al[4] reported a prevalence rate of 32.9% with a slight female preponderance. Spinal meningioma has also been reported in the literature with a 30.8% prevalence in a study done in South-East Nigeria[5]. Two independent studies conducted in Ghana and Egypt also reported meningiomas as the second most common intracranial tumours second to gliomas with prevalence rates of 36.2%[6] and 35.2%[7] respectively. In India and the USA, prevalence rates of 23.2%[8] and 33.8%[9] were reported. The prevalence of meningioma in the paediatric age group is generally low ranging between 5.4% to 6.7% from studies done in Nigeria[10,11]. The rise in the incidence of intracranial meningioma in Nagasaki Atomic bomb survivors is suggestive of a strong correlation between radiation exposure and the development of meningioma in the population[12]. Recent data from the USA reported that the incidence of meningiomas was higher in blacks compared to whites, American Indian and Alaska Natives (AIAN) and Hispanics[13]; however, higher survival rates have been reported in white patients compared to non-white patients.[14] The reason for this disparity may be multifactorial and include differences in socioeconomic status, insurance status, cultural beliefs, genetic factors, quality and extent of surgical resection, quality of treatment facilities, access to treatment, proper post-op imaging and follow-up care[14]. Some familial syndromes have been associated with meningiomas like Neurofibromatosis type 2 syndrome, Nevoid basal cell carcinoma syndrome, Cowden syndrome, Werners syndrome, and BAP1 tumour predisposition syndrome[15]. Meningioma is also a common site of systemic tumour-to-tumour metastasis from the gastrointestinal tract and prostate gland[16].

Meningiomas are rare tumours in the paediatric age group, though more common in older children, Ostrom et al[17] reported a prevalence rate of 2% in the report for the Central Brain Tumour Registry of the United States of America (CBTRUS) when compared to other intracranial tumours. Olasode et al[11] in Southwest Nigeria reported a prevalence rate of 6.7%, compared to other intracranial lesions in the paediatric age group. Some other studies in the United States of America and China reported a prevalence rate of <5% [18] and <3%[19] respectively. Although there is a marked female preponderance of meningioma in the adult age group, Kotecha et al[20] reported a male preponderance in the paediatric age group.

Meningiomas frequently occur in adults. Mezue et al[21]observed a peak incidence in the fifth and sixth decades for males and females respectively. In the CBTRUS report, a rising incidence with an increase in age was reported with meningioma being the commonest CNS tumour from 35 – 85+ years, constituting about 36.1% of the central nervous system tumours[17].

The anatomic sites of meningiomas vary within the central nervous system. An independent study done by Shah et al[22] reported convexity to be the most common site of occurrence with a prevalence rate of 60%. However, a study done in Enugu, South East Nigeria by Mezue et al[21] reported the olfactory groove as the most common location with a prevalence rate of 26.5%, closely followed by convexity tumours with a 23.5% occurrence rate.

Meningiomas are believed to originate from the meningothelial cells. The aetiology and risk factors of meningiomas can be divided into genetic and non-genetic factors including environmental factors, hormonal factors and radiation[9].

Two non-genetic factors have been mostly related to the growth of meningiomas, hormones and radiation. Hormone replacement therapy (HRT) has been observed as a positive risk factor for meningiomas. Benson et al[23] in their study, observed a higher risk of all CNS tumours, including meningiomas among oestrogen-only HRT users, compared to users of oestrogen-progesterone HRT users.

Radiation-induced meningioma (RIM) has received recognition as a pathologic entity. Chourmouzi et al[24] reported a case of meningiomas

Developing in a young male, 19 years post-irradiation. Due to the increased presence of RIM in some families more than others, Hosking et al[25] observed that radiosensitivity was determined through the co-inheritance of multiple risk alleles. Also, a strong correlation between radiation exposure and increased meningioma incidence in Nagasaki bomb survivors was reported.[12]

Other non-genetic risk factors that have been proposed include a history of uterine fibroids as reported by Yen et al[26]. Head trauma, cell phone use, occupation, diet and allergy reviewed by Wiemels et al[9], and other preexisting conditions like epilepsy, diabetes and stroke as reported by Schwartzbaum et al[27], largely showed inconsistent results. However, a population-based study by Kuan et al[28] observed that an increased risk of meningiomas is not associated with a head injury. Lead exposure has also been reported as a risk factor for meningiomas[29].

Genetic Profiles as Risk Factors in Meningiomas

Inactivating mutations of the tumour suppressor gene, Neurofibromatosis-2 (NF-2), located on the long arm of chromosome 22 is the commonest genetic alteration associated with sporadic intracranial meningiomas.[30] This mutation is present in about 30% of all three WHO grades of meningiomas[31]. NF-2 gene encodes the Merlin protein which plays a role in the regulation of cell growth. Loss of function mutations in the NF-2 gene plays a key role in meningioma tumorigenesis [9]. Other non-NF-2 mutations have been discovered in meningiomas and are mostly located in low-grade tumours. The two classes as proposed by Clark et al[32] are

1. Benign skull base meningiomas mostly harbour mutations in the TRAF 7, KLF 4, AKT 1 and SMO genes. These molecular signatures are, however, distinctively absent in paediatric meningiomas[33].

2. Higher-grade tumours of the cerebral and cerebellar hemispheres tend to harbour NF-2 gene mutations[30].

Cumulative chromosomal abnormalities have been associated with atypical and malignant meningiomas. The chromosomal losses on 1p, 6q, 10q, 14q, 18q and gains on 1q, 9p, 12q, 15q, 17q play key roles in meningioma progression[30].

This study aims to compare the common histopathological subtypes of meningiomas seen in our population with the age and sex of the patients and compare them with those seen in other populations and races.

Materials And Methods

Five hundred and thirty-nine intracranial and spinal tumours that were histologically diagnosed between 2009 and 2018 at the University of Nigeria Teaching Hospital, Enugu, Nigeria were reviewed. Meningiomas constituted one hundred and thirty cases of which 107 cases were included in the study.

Patients' age, sex, tumour location, and WHO grades were analysed in this study. The tumour location was defined based on MRI images and neurosurgical description. The surgical specimens were reviewed independently by two pathologists and the WHO grade was defined by the 2020 WHO Classification for Meningiomas. The specimens were fixed in 10% neutral buffered formalin, embedded in paraffin and cut into thin sections of 4mm thickness.

Histological features that were assessed included whorl formation, presence of psammoma bodies, vascularity, mitosis, macro nucleoli, nuclear pleomorphism, formation of sheets, presence of foam cells, presence of clear cells, papillary change and brain invasion.

The Psammoma variant was considered if the tumour comprised 50% and above of psammoma bodies.

Sheet formation was assessed by the absence of any particular growth pattern.

Brain invasion was defined by the finger-like invasion of tumour cells into the surrounding brain parenchyma.

An angiomatous variant was considered when blood vessels composed 50% or more of the tumour.

All procedures performed in the current study were approved by the University of Nigeria Teaching Hospital IRB (NHREC/05/01/2008B-FWA00002458-1RB00002323; 12th February 2020) following the 1964 Helsinki Declaration and its later amendments.

Formal written informed consent was not required with a waiver by the appropriate IRB.

Results

Five hundred and thirty-nine (539) CNS neoplasms were seen during the study period with a prevalence of 4.9% of all the neoplasms seen within the study period. Of these, meningiomas constituted 130 cases with a prevalence of 1.2% of all the neoplasms seen within the study period and 24.1% of all the CNS neoplasms seen within the study period. One hundred and seven cases of meningiomas met the inclusion criteria for this study. Table I shows the overall age and sex distribution of meningioma. The ages ranged from 6 years to 88 years [SD ± 16.54]. The peak age of occurrence was in the 41 - 50 years [SD ± 16.54] age group (23.4%) and was closely followed by a 19.6% prevalence in the 51 – 60 years [SD ± 16.54] age group. Also, this study revealed a slight female preponderance with female to male ratio of 1.4:1.

Table I: The overall characteristics of patients

Variables	Frequency (n = 107)	Percent (100)
Age (years)		
1-10	1	0.9
11-20	5	4.7
21-30	9	8.4
31-40	19	17.8
41-50	25	23.4
51-60	21	19.6
61-70	18	16.8
71-80	7	6.5
81-90	2	1.9
Mean age(SD)	48.39(16.54)	
Sex		
F	62	57.9
M	45	42.1
F:M	1.4:1	

Table II shows Fibrous meningioma as the commonest variant overall, with the uncommon occurrence of meningiomas in the first two decades of life. The cerebral convexity was found to be the commonest location; however, the intra-orbital location was commoner in the younger age groups.

Table III shows the distribution of diagnoses and locations based on the WHO grades. The fibrous variant was found to be the variant among the WHO grade 1 subtype with a prevalence of 30.9%. The Meningothelial, Psammomatous and Transitional subtypes were found to Have a prevalence of 24.5%, 22.3% and 18.1% respectively. The commonest location across all the WHO grades was the cerebral convexities, 80.9% for WHO grade 1, 62.5% for WHO grade 2 and 100% for WHO grade 3.

Table II: Distribution of Diagnosis and location based on age

Diagnosis/Type	Age(years)								
	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Grade 1									
ANGIOMATOUS MENINGIOMA	0(0.0)	0(0.0)	1(11.1)	0(0.0)	0(0.0)	1(4.8)	1(5.6)	0(0.0)	0(0.0)
FIBROUS MENINGIOMA	1(100)	0(0.0)	2(22.2)	9(47.4)	8(32.0)	4(19.0)	4(22.2)	0(0.0)	1(50.0)
MENINGOTHELIAL MENINGIOMA	0(0.0)	1(20.0)	1(11.1)	2(10.5)	8(32.0)	3(14.3)	6(33.3)	2(28.6)	0(0.0)
MICROCYSTIC MENINGIOMA	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(4.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
PSAMMOMATOUS MENINGIOMA	0(0.0)	2(40.0)	4(44.4)	1(5.3)	2(8.0)	4(19.0)	4(22.2)	3(42.9)	1(50.0)
TRANSITIONAL MENINGIOMA	0(0.0)	1(20.0)	0(0.0)	4(21.1)	4(16.0)	4(19.0)	3(16.7)	1(14.3)	0(0.0)
Grade 2									
ATYPICAL MENINGIOMA	0(0.0)	0(0.0)	1(11.1)	2(10.5)	1(4.0)	1(4.8)	0(0.0)	1(14.3)	0(0.0)
CLEAR CELL MENINGIOMA	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(4.0)	1(4.8)	0(0.0)	0(0.0)	0(0.0)
Grade 3									
PAPILLARY MENINGIOMA	0(0.0)	1(20.0)	0(0.0)	1(5.3)	0(0.0)	3(14.3)	0(0.0)	0(0.0)	0(0.0)
Location									
FORAMEN MAGNUM	0(0.0)	1(20.0)	0(0.0)	0(0.0)	0(0.0)	1(4.8)	0(0.0)	0(0.0)	0(0.0)
CEREBRAL CONVEXITIES	1(100)	1(20.0)	6(66.7)	15(78.9)	25(100)	17(81.0)	15(83.3)	4(57.1)	2(100)
INTRAORBITAL	0(0.0)	2(40.0)	0(0.0)	1(5.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
NASAL CAVITY	0(0.0)	0(0.0)	1(11.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
OLFACTORY GROOVE	0(0.0)	0(0.0)	0(0.0)	1(5.3)	0(0.0)	1(4.8)	1(5.6)	1(14.3)	0(0.0)
SELLA TURCICA	0(0.0)	0(0.0)	1(11.1)	0(0.0)	0(0.0)	1(4.8)	0(0.0)	0(0.0)	0(0.0)
SPINAL	0(0.0)	1(20.0)	1(11.1)	2(10.5)	0(0.0)	1(4.8)	2(11.1)	2(28.6)	0(0.0)

Table III: Distribution of Diagnosis and location based on grade

Variables	Grade 1 (n =94)	Grade 2 (n =8)	Grade 3 (n = 5)
	n(%)	n(%)	n(%)
Diagnosis/Type			
Grade 1			
ANGIOMATOUS MENINGIOMA	3(3.2)	0(0.0)	0(0.0)
FIBROBLASTIC MENINGIOMA	29(30.9)	0(0.0)	0(0.0)
MENINGOTHELIAL MENINGIOMA	23(24.5)	0(0.0)	0(0.0)
MICROCYSTIC MENINGIOMA	191.1)	0(0.0)	0(0.0)
PSAMMOMATOUS MENINGIOMA	21(22.3)	0(0.0)	0(0.0)
TRANSITIONAL MENINGIOMA	17(18.1)	0(0.0)	0(0.0)
Grade 2			
ATYPICAL MENINGIOMA	0(0.0)	6(75.0)	0(0.0)
CLEAR CELL MENINGIOMA	0(0.0)	2(25.0)	0(0.0)
Grade 3			
PAPILLARY MENINGIOMA	0(0.0)	0(0.0)	5(100.0)
Location			
FORAMEN MAGNUM	2(2.1)	0(0.0)	0(0.0)
CEREBRAL CONVEXITIES	76(80.9)	5(62.5)	5(100.0)
INTRAORBITAL	3(3.2)	0(0.0)	0(0.0)
NASAL CAVITY	1(1.1)	0(0.0)	0(0.0)
OLFACTORY GROOVE	4(4.3)	0(0.0)	0(0.0)
SELLA TURCICA	2(2.1)	0(0.0)	0(0.0)
SPINAL	6(6.4)	3(37.5)	0(0.0)

In comparing the distribution of the diagnoses and location based on sex, Fibrous and Psammomatous meningiomas were the commonest variants seen in females as shown in Table IV. Fibrous and Transitional variants were the commonest in males. The meningothelial variant was the third most common variant seen in males and females. The cerebral convexities were also found to be the commonest location in males (77.8%) and females (82.3%).

Table IV: Distribution of Diagnosis and location based on Sex

Variables	Female (n=62)	Male (n=45)
	n(%)	n(%)
Diagnosis/Type		
Grade 1		
ANGIOMATOUS MENINGIOMA	0(0.0)	3(6.7)
FIBROBLASTIC MENINGIOMA	17(27.4)	12(26.7)
MENINGOTHELIAL MENINGIOMA	14(22.6)	9(20.0)
MICROCYSTIC MENINGIOMA	1(1.6)	0(0.0)
PSAMMOMATOUS MENINGIOMA	17(27.4)	4(8.9)
TRANSITIONAL MENINGIOMA	6(9.7)	11(24.4)
Grade 2		
ATYPICAL MENINGIOMA	2(3.2)	4(8.9)
CLEAR CELL MENINGIOMA	2(3.2)	0(0.0)
Grade 3		
PAPILLARY MENINGIOMA	3(4.8)	2(4.4)
Location		
FORAMEN MAGNUM	2(3.2)	0(0.0)
CEREBRAL CONVEXITIES	51(82.3)	35(77.8)
INTRAORBITAL	2(3.2)	1(2.2)
NASAL CAVITY	0(0.0)	1(2.2)
OLFACTORY GROOVE	3(4.8)	1(2.2)
SELLA TURCICA	1(1.6)	1(2.2)
SPINAL	3(4.8)	6(13.3)

Discussion

The three histological grades of meningioma were assessed in this study. One hundred and seven (107) histologically confirmed cases of meningioma were studied. This study found that the meningiomas were most prevalent in individuals between 41 – 50 years [SD ± 3] of age, constituting 23.4% of the cases. This is in agreement with the study done by Bhat et al[34] which reported a peak age of 41 – 50 years. The study by Karim et al[35] in Bangladesh also reported the highest prevalence rate in the 41 – 50 years age group in their results. This study is also in partial agreement with that by Mezue et al[36] which reported 41 – 50 years as the peak age range for males and 51 – 60 years as the peak age range for females. However, Ikeri et al[37] in Lagos, Nigeria reported a peak age occurrence of 31 – 40 years. This variance may be accounted for by the smaller sample size that was used in the study.

The present study revealed a female preponderance (57.9%) which agrees with most other studies that have been reported[37,38]. However, Olasode et al[2] reported a slight male preponderance in their study conducted in Ibadan, Nigeria. In this study, a total of 210 intracranial neoplasms (including primary and secondary neoplasms) were studied and meningioma was found to be the third most commonest tumour with a sample size of 24. The small sample size may have accounted for the variation that showed the slight male preponderance.

This study also found that WHO grade 1 meningiomas are the commonest grade (87.9%) followed by WHO grade 2 (7.5%), and the least observed is WHO grade 3 (4.6%). A hospital-based study done by Mezue et al[36] in Enugu, Nigeria reported 84.7% for WHO grade 1 tumours, 2.6% of WHO grade 2 tumours and 5.1% for WHO grade 3 tumours. In their study, three (3) out of the sixty-eight (68) cases studied were unclassified. Ikeri et al[37] in their study in Lagos, Nigeria reported 86.1% for grade WHO grade 1, 11.1% for WHO grade 2 and 2.8% for WHO grade 3. In a hospital-based study in Iran, Samadi et al[39] reported 86.1%, 8% and 5.9% for WHO grades 1, 2 and 3 respectively. This slight variation in percentages may be due to the generally small sample size of WHO grade 2 and 3 meningiomas assessed in the individual studies.

This study showed that the commonest subtype was the fibrous variant with a prevalence of 27.1%. This is similar to the findings by Lakshmi[40] in India. It is however at variance with findings in Lagos and Enugu, Nigeria that reported Meningothelial and Psammomatous variants as the commonest variants from their independent studies respectively.[36,38] Telugu et al[41] observed that the Meningothelial variant was the commonest variant in their study. This variance may be accounted for by the varying sample sizes of various independent studies and the varying locations of the studies.

Inter-observer variation can also account for this variance as there is a lack of standardisation of the parameters used in the classification of meningiomas into subtypes in the current WHO 2020 classification. This can result in marked variation in diagnoses of these sub variants, especially in the WHO grade 1 subtypes. Other common variants that were observed in this study include Meningothelial (21.5%), Psammomatous (18.7%) and Transitional (15.9%) variants.

The convexities were observed to be the commonest location of the tumour in this study, similar to reports from China.[42] However, an independent study done by Mezue et al[36] in Enugu, Nigeria reported the olfactory groove as the commonest location. This variance may be due to the use of surgical techniques that allow better visibility of tumour extensions to the olfactory groove.

In this study, a case of nasal cavity meningioma was seen in a male patient in the 21 – 30 years age group. A case report by Rai et al[43] reported nasal meningiomas in patients in a 28-year-old female. The nasal cavity is an uncommon location for meningiomas as was seen in this study.

The WHO grade 3 meningiomas were all located in the convexities in this study. This is in keeping with a study done by Kane et al[44] in the USA that found that the convexities had the highest percentage of WHO grade II/III tumours combined. In addition, WHO grade II and III tumours were found to be less common in individuals above 60 years of age in this study. However, another study from China showed no correlation between age groups and WHO grades of meningioma[45].

Spinal meningiomas were found to be more common in males in this study. However, an independent study in Canada by Westwick et al[46] reported significant female preponderance but higher male mortality. This variation may be due to the limited sample size of this study.

In this study, it was found that meningiomas had a low prevalence in the first two decades of life, constituting 5.6% of the number of cases studied with an M: F ratio of 1:2. Ikeri et al[37] in Lagos, Nigeria reported a 2.8% occurrence in the paediatric age group. A study done in the USA reported higher male preponderance[47].

Another study from the USA reported a 3.7% occurrence of meningiomas among diagnosed paediatric brain tumours within their study period[48].

Intraorbital tumours were also found in younger patients in our study. Two out of the three Intraorbital tumours seen in our study were found in the paediatric age group while one was found in the 31 – 40 [SD ± 16.54] years age group. This is following a study done in the USA that reported a younger age of presentation for Intraorbital meningiomas[49].

In conclusion, Meningiomas are a diverse group of CNS tumours with significant micromorphological interconnection in WHO grades 1 and 2. The parameters for the assignment of grade and sub variants need to be standardised for accurate classification of these tumours. Also, there is room for more research in tumour biology and genetic signatures of each subvariant as these may potentially be applied in patient management for complicated cases.

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What does this study add to existing knowledge?

This study shows that the commonest variant of meningiomas in our population is the fibrous variant and a higher percentage of this variant has been reported to be progesterone receptor negative. This should be taken into account in consideration of the use of anti-progestins as an option for chemotherapeutic treatment in non-operable meningiomas in our population

As it may not be an effective option. Also, this study shows that the use of P63 for grading meningiomas is not an effective tool and should not be relied on in patient management in our population. However, more research is needed to fully understand the tumour biology.

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