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## Research Article

### CD44 EXPRESSION IN SUDANESE MENINGIOMA PATIENTS

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#### ABSTRACT

Meningiomas are predominantly benign tumors, which arise from the arachnoids' cap cells. The development mechanism is unknown but they may result from an adverse effect of cranial irradiation and trauma. Recently Arbab et al reported in a study done at the National Center of Neurological Sciences, Khartoum Sudan, the incidence of meningioma was found to be more than 65% of all intra cranial neoplasms. **Material and methods:** This is a cross-sectional hospital base study that had been performed at the National Center for Neurological Sciences during March 2015 to October 2015. Tumor specimens were obtained from 21 intracranial meningiomas treated at the National Center for Neurological Sciences. All tumors were classified according to the WHO guidelines (2007). **Results:** In this study strong expression of cd44 was observed in 75% of the fibrous G 1 meningioma, and 100% of the atypical G 11.

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## INTRODUCTION

Meningiomas are predominantly benign tumors, which arise from the arachnoids' cap cells [1]. The development mechanism is unknown but they may result from an adverse effect of cranial irradiation and trauma [2]. Meningiomas may occur intracranially or within the spinal canal in some cases. In Africa, the frequency of meningiomas is even higher and reaching 30% of all brain tumors. This race differences extend to Africans Americans as reports indicate more meningiomas incidence among Africans Americans compared with white Americans. In Sudan, Abu salih and Abdul-Rahman (1988) reported similar results in a material of 127 cerebral tumors during 10 years time [3]. Recently Arbab et al reported in a study done at the National Center of Neurological Sciences, Khartoum Sudan, the incidence of meningioma was found to be more than 65% of all intra cranial neoplasms.[4]. Meningiomas are usually globular in shape and well-demarcated neoplasms. They have a wide dural attachment and invaginate into the underlying brain without invading it. Their cut surface is either translucent pale or homogeneously reddish brown. The three

most common histological subtypes of meningiomas are the meningothelial (syncytial), transitional, and fibroblastic meningiomas. Meningothelial meningiomas reveal densely packed cells that are arranged in sheets with no clearly discernible cytoplasmic borders [5]. Although not prominent, whorls are present (calcified whorls are termed psammoma bodies). Fibroblastic (fibrous) meningiomas reveal sheets of interlacing spindle cells. The intercellular stroma is composed of reticulin and collagen. The transitional variety reveals features common to both, the meningothelial and fibroblastic varieties; others include angiomatous, microcystic, secretory, clear cell, choroid, lymphoplasmacyte-rich, papillary, and metaplastic variants. According to the World health organization (WHO) classification of tumors, meningiomas are classified into three grading type Grade I benign, Grade II atypical and Grade III anaplastic.

The cell surface glycoprotein cd44 is a multifunctional receptor that is expressed on most human cells. Normally, cd44 is crucial for regulating of cell adhesion, proliferation, migration, angiogenesis, inflammation, and cell signaling[6].it is principal

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ligand is found hyaluronan is an important component that is also abundant in brain tissue.[7, 8]. several studies that cd44 expression was found to be associated with aggressive and invasive cancers [9], suggesting that cd44 may act as a cell surface receptor for proteolytically active MMP-9 [10]. In meningioma anti cd44 antibodies stains lower grade of tumors weaker than they stain meningiothelial and transitional subtypes and higher grade tumors.[10, 11, 12, 14, 15]. few studies have addressed the relationship between brain-invasive growth and cd44 expression in meningioma without finding a clear association.[11, 12]. In the present study we aimed To identify cd44 proteins immunostaining in intracranial meningioma among Sudanese patients, and to correlate the biological behavior of meningioma tumors with the cd44 proteins in intracranial meningiomas among Sudanese patients.

**MATERIAL AND METHODS**

This is a cross-sectional hospital base study that had been performed at the National Center for Neurological Sciences during March 2015 to October 2015.

In this study samples were obtained from intracranial meningioma diagnosed histologically at the National Center of Neurological Sciences, during the above mentioned period. The study was conducted in accordance with the guidelines of the local ethical committee. Tumor specimens were obtained from 21 intracranial meningiomas’ treated at the National Center for Neurological Sciences. All tumors were classified according to the WHO guidelines (2007). Tissue samples were taken in sterile containers, that contains neutral buffered formalin, then processed for detection of cd44 proteins in intracranial meningiomas among Sudanese patients.

Clinical and demographic data were collected using predesigned structured interview questionnaire. The personal data of all patients were obtained from the registry data base in the National Center of Neurological Sciences, and the laboratory data were collected from meningioma immunostaining for cd44 proteins in intracranial meningiomas among Sudanese patients.

The following variables concerning each case were recorded (age, gender, tribe, histopathology of tumor, WHO criteria, immunostaing of cd44)

Accordin to Dako standard protocol for immunostaining 21 intracranial meningioma tissue from archived paraffin embedded blocks were sectioned, special immunostaining slides were used, 4 µl sections were obtained, and then incubated in the oven at 65 °C for overnight. The sections were then treated with xyline, absolute ethanol, 90% ethanol, 70% ethanol, respectively and washed in water, then in retrieval solution at 95 °C in water bath for 30 minutes. Dako pen was used for drawing a circle around the reaction area on the slides, all slides were placed in washing buffer for 10 minutes, and then hydrogen peroxide was performed to all sections for peroxidase blocking, and then washed in washing buffer for 15 minutes. The primary antibody against cd44 protein was added to all sections for 30 minutes, then washed in buffer for 15 minutes, followed by link solution ( HRP ) for 25 minutes , washed in buffer for 15 minutes, and then diluted DAB solution was added for 10 minutes, then washed twice in water and washing buffer respectively. After that Mayers

hematoxylin was used as a counter stain, then after the cover slips and DPX mounting medium were used for mounting and preserving sections. All sections were examined under the light microscope. Expression of cd44 proteins immunoreactivity was reported as strong, moderate and weak.

Data were analyzed using the Statistical Package for Social Sciences (SPSS) 13 software with reference P.value of 0.05 considered statistically significant.

**RESULTS**

The present study included 21 intracranial meningioma patients, 38.1% of studied materials were males while females constituting 61.9%, with male to female ratio 1:1.6, (Table.1). The age group 41 to 50 years constituting 52.4% was the most affected age group (Table 2). Results of this study showed that, meningiomas were more common in Afro Asiatic tribes, 15 patients (71.4%), followed by Nilo Saharan in 3 patients (14.3%) and 3 in Niger Congo tribes (Table3). Olfactory groove and frontal meningioma showed the highest percent of tumor location (13.3%). (Table4). WHO grading scale (2007) identified grade 1 meningioma in 81%, of the patients and grade 11 in 19%. (Table5).

**Table 1** shows frequency of male and female

Sex	Frequency	Percent
Male	8	38.1%
Female	13	61.9%
Total	21	100%

**Table 2** shows age in group of studied materials

ge group	Frequency	Percent
21-30 years	2	9.5%
31-40 years	11	52.4%
41-50 years	3	14.3%
51-60 years	3	14.3%
61-70 years	3	14.3%
Total	21	100%

**Table 3** shows linguistic affiliations of different Sudanese tribes

Linguistic affiliation	Frequency	Percent
Afro-Asiatic	15	71.4%
Nilo-Saharan	3	14.3%
Niger-Congo	3	14.3%
Total	21	100%

**Table 4** shows the anatomical location meningioma

Anatomical location	Frequency	percent
temporal	3	14.3
olfactory	5	23.8
sagittal	1	4.8
sellar	2	9.5
convexity	1	4.8
cerebellar	1	4.8
frontal	5	23.8
sphenoid	2	9.5
para sagittal	1	4.8
Total	21	100.0

**Table 5** shows the WHO grade of meningioma

Grade	Frequency	Percent
G1	17	81.0
G2	4	19.0
Total	21	100.0

In this study histological classification revealed that, the fibrous variant was mostly encountered (38.1%), followed by mixed in 23.8% of the cases and in 19% the pathology was

atypical (Table6). The immunostaining results of cd44 were displayed in Tables (7). Positive immuno-staining for cd44 was identified in all of the patients. Strong positivity of cd44 was encountered in 75% and 100% of the fibrous and atypical meningiomas respectively. The correlation between cd44 expression and histological types of meningioma was statistically significant  $P= 0.014$  (Tables 8)

**Table 6** shows histological subtypes of meningioma in this study

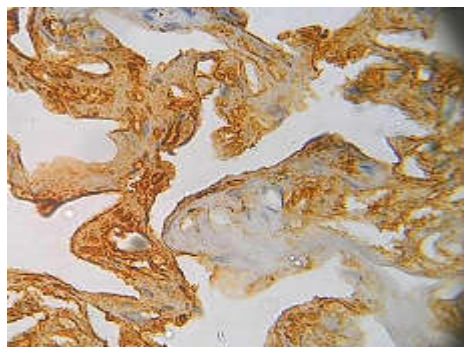
Histopathology	Frequency	Percent
fibrous	8	38.1
atypical	4	19.0
meningiothelial	1	4.8
psammomatous	2	9.5
angiomaticous	1	4.8
mixed	5	23.8
Total	21	100.0

**Table 7** shows cd44 expression in meningioma

Cd44 expression	Frequency	Percent
strong	12	57.1%
moderate	6	28.6%
weak	3	14.3%
Total	21	100%

**Table 8** shows cross tabulation between cd44 expression and meningioma subtypes

Cd44	Histopathology						total
	fibrous	atypical	meningiothelial	psammomatous	angiomaticous	mixed	
Strong	6	4	0	0	0	2	12
Moderate	2	0	1	0	1	2	6
Weak	0	0	0	2	0	1	3

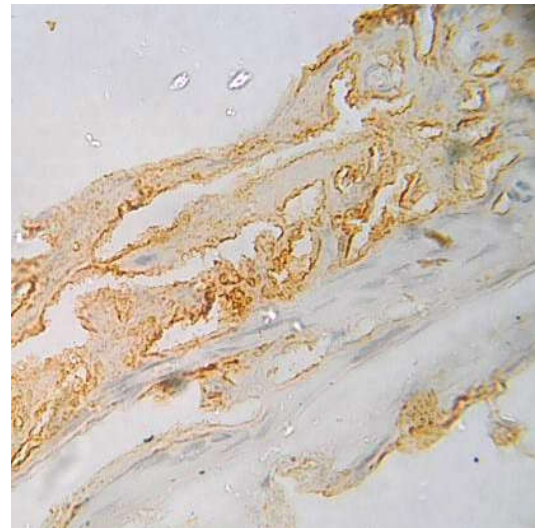


A



B

**Fig. 1** shows strong expression of cd44 in fibrous meningioma(a), and moderate expression of cd44 (b).



**Fig 2** cd44 expression in atypical meningioma

## DISCUSSION

The findings of this study showed that among the 21 patients been studied, 13 patients were female with female: male ratio of 1.6:1.  $P>0.000$ , The female predominance has been suggested to be hormonal dependent (16), however, in a Turkish study it was postulated that the high incidence of meningioma in women can not be explained only by difference of sex hormone receptors and thus other hidden causes should be looked for, [17].

The participants ages in this study revealed that 81% of the patients were above the age of 40 years, this finding did not differ from the international incidence of intracranial meningioma among age group in male and females [17, 18, 19].

In this study meningioma incidence was correlated well with the linguistic affiliation of the different Sudanese tribes. The most affected group in the present study was the Afro-Asiatic tribes. This finding could not be attributed to the geographical location of these tribes since members of the same tribe living in distant geographical areas have the tendency to develop meningioma. This is further supported by the finding that members of tribes affiliated to the other linguistic groups and sharing the same geographical locations with Afro-Asiatic tribes, did not report to have the same incidence of the disease.

The cell surface glycoprotein cd44 is a multifunctional receptor that is expressed on most human cells. Normally, cd44 is crucial for regulating of cell adhesion, proliferation, migration, angiogenesis, inflammation, and cell signaling[6]. it is principal ligand is found hyaluronan is an important component that is also abundant in brain tissue.[7, 8].several studies howed that cd44 expression was found to be associated with aggressive and invasive cancers [9], suggesting that cd44 may act as a cell surface receptor for proteolytically active MMP-9 [10]. In meningioma anti cd44 antibodies stains lower grade of tumors weaker than they stain meningiothelial and transitional subtypes and higher grade tumors.[11, 12, 13, 14, 15]. few studies have addressed the relationship between brain-invasive growth and cd44 expression in meningioma without finding a clear association.[10, 11].

The findings of the present study have indicated that fibrous meningioma, atypical meningioma showed similar pattern of cd44 marker expression. Furthermore 75% of the fibrous meningiomas in this study strongly expressed cd44 immunostaining and 4 atypical meningioma which constituting 100% were showed similar cd44 expression. A study done by S O Suzuki, T Iwaki, T Kitamoto showed that only secretory meningioma was strongly expressed cd 44 in 4 cases, out of 23 of meningioma tumors.[20]. Another study revealed that atypical, meningiothelial and transitional subtypes of meningioma were cd44 positive immunoreactivity, and negative cd44 for fibrous subtype of meningioma.[21] In 1997 Figarella-Branger *et al.* found that strong CD44s expression was associated with meningothelial and transitional meningiomas and was lower in the fibroplastic one.[11] Study from Bucharest, Romania, indicated cd44 immunoreactivity was detected in 56.6%, 63.8% of G 1 and G11 meningioma respectively.[23] In this study strong expression of cd44 was observed in 75% of the fibrous G 1 meningioma, and 100% of the atypical G 11. The findings of the present study showed that, out of the fifteen meningioma subtypes, only six variants were identified, of these the fibrous was the most common. More over, clear discrepancy was noted between the fibrous and atypical sub types.

Though the fibrous meningioma is considered to be benign, however, its biological behavior seemed to be more aggressive. This has been manifested either by the relatively large tumor volumes or the aggressive behavior as revealed by the images. The findings of this study showed that 75% of the fibrous meningioma was expressed cd44 protein; this may consolidate the aggressive biological behavior of this type of meningioma. The feature of aggressiveness of fibrous was been observed in study done at the National Center of Neurological Sciences, Khartoum Sudan, in which they investigated Ki 67 antigen immunohistochemistry in intracranial meningioma, their findings revealed that the fibrous variant was expressed the highest Ki 67 labeling index similar to atypical meningioma.[24] The findings of this study and the above mentioned one may indicate that the fibrous meningioma in Sudan behave biologically as the atypical meningioma, and this findings needs more investigation on bigger sample size to confirm the results.

## CONCLUSION

In this study strong expression of cd44 was observed in 75% of the fibrous G 1 meningioma, and 100% of the atypical G 11. Out of the fifteen meningioma subtypes, only six variants were identified, of these the fibrous was the most common.

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