VALUE OF MRI (DWI &ADC) IN DIFFERENTIATING BENIGN AND MALIGNANT ORBITAL LESIONS

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ABSTRACT:

Background: *Orbital and intraocular masses are relatively uncommon compared to other mass lesions of the body. It has been described that two-thirds of orbital tumors are benign and one third is malignant. Differentiating between these causes based on clinical findings may be difficult. Some lesions can be diagnosed easily depending on their characteristics on MRI but sometimes their characterization is still difficult. Diffusion weighted imaging (DWI) is an advanced MR-based technique which has the ability to characterize and differentiate morphologic features by measuring differences in apparent diffusion coefficient (ADC) and so can aid in differentiation of malignant and benign orbital lesions, which is focal to planning further patient management.*

Aim of the work: *Is to investigate the utility of DW-MRI images and generated ADC values in the differentiation between benign and malignant orbital masses.*

Patient and Methods*: This study included 21 cases (13 females and 8 males) proven to have an orbital mass by an available radiological study.*

Results: *Of the 21 subjects, 10 out of 11 malignant lesions were correctly classified as malignant (TP) & all of the 10 benign lesions were correctly classified as benign (TN). A sensitivity of 90.9 % was achieved, with a specificity of 100 %. The Positive predictive value was 100 %, while the negative predictive value was 90.9%.*

Conclusion: *DWI and ADC maps with ADC value calculations are useful for differentiating between malignant and benign orbital tumors. Apparent diffusion coefficient value can solve some clinical problems of the orbit that affect patient management.*

Keywords: *Orbit; Diffusion weighted MRI; ADC; Benign; Malignant masses.*

INTRODUCTION:

Orbital and intraocular masses are relatively uncommon compared to other mass lesions of the body. It has been described that two-thirds of orbital tumors are benign and one third is malignant .(1)

Differentiating between these causes based on clinical or traditional radiographic findings may be difficult.(2)

Magnetic resonance imaging (MRI) may help in characterization of the various orbital masses as there are some pathognomonic features for particular masses. But for cases without these pathognomonic characteristics it remains difficult to deliver a diagnosis based on MR imaging features because there are often unspecific and overlapping imaging findings. Aggravating this situation, rare tumor entities are unexpected and therefore may be misdiagnosed.(1)

Diffusion weighted imaging (DWI) is an MR-based technique in which dedicated phase-defocusing and -refocusing gradients allow evaluation of microscopic water diffusion within tissues. It has been considered a means to characterize and differentiate morphologic features, including edema, necrosis, and tumor tissue, by measuring differences in apparent diffusion coefficient (ADC) caused by water proton mobility alternations.(3)

Diffusion-weighted MR imaging has been used for differentiation between benign and malignant head and neck masses, cervical lymph nodes, parotid tumors, and thyroid nodules. A few studies discussed the role of diffusion MR imaging in the diagnosis of malignant orbital tumors, the differentiation of lymphoma from pseudo tumor and other orbital masses, the assessment of orbital cellulitis, as well as in the characterization of optic nerve lesions.(4)

AIM OF THE WORK:

The aim of this study is to investigate the utility of DW-MRI images and generated ADC values in the differentiation between benign and malignant orbital masses.

PATIENTS AND METHODS:

This study was conducted from December 2019 to September 2020 and included 21 patients (13 females and 8 males).

Inclusion criteria:

Patient of any age and of either sex proven to have an orbital mass by an available radiological study.

Exclusion criteria:

- Patients with contraindications to MRI, e.g. an implanted magnetic device, pacemakers or claustrophobia.
- Patients with contraindication to contrast media e.g. elevated renal functions.
- Patients who underwent previous surgery for the current orbital mass and patients who received chemotherapy or radiotherapy.

Official permission was obtained from the radio diagnosis department, faculty of medicine Ain-Shams University and informed consents were obtained from all patients or their legal guardians if they were younger than 18years.

Study procedures:

- ***After obtaining full medical history and checking serum creatinine, all patients underwent magnetic resonance imaging on a 1.5-T MR system (Achieva; Philips).***

An attending anesthesiologist was responsible for administration of sedation and any preparation required prior to that if the patient was unable to remain stationary throughout the procedure.

- The sequences of conventional MRI orbit protocol were taken; Axial T1WI, Axial T2WI, Axial STIR, Coronal TIWI, Coronal T2WI. This was followed by intravenous administration of Gadolinium- DTPA (0.3 mg/kg), and contrast enhanced T1WI in axial, coronal and sagittal planes.
- Then Diffusion-weighted MR imaging was obtained using a multi section single-shot echo planar imaging sequence with b values of 0 and 800 s/mm ^{2}. The ADC maps were generated automatically by the MRI software.

Image analysis:

- Conventional images were analyzed for localization of the lesions and identification of solid non necrotic, non-

hemorrhagic, non-calcified enhancing part of the tumors.

- Qualitative assessment of signal intensity of the solid parts of the lesions, relative to surrounding ocular muscles was done and were described as either hyperintense, isointense, or hypointense. A lesion was designated as restricted if it showed high signal intensity on b value 800 images and low signal intensity on the corresponding ADC map.
- Quantitative analysis was done by drawing (ROI) around the margin of the solid, enhancing part of the orbital mass, taking care to exclude cystic, necrotic, calcified and hemorrhagic areas and average ADC value was calculated.

Statistical analysis:

The data were analyzed using Statistical Package for Social Science (IBM Corp, released 2013. IBM SPSS statistics for windows, V. 22.0. Armonk, NY. USA). Parametric quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were described as frequency and percentage. The categorical variable was analyzed with Fisher's Exact Test and Pearson Chi-Square test. Independent sample t test was used for parametric quantitative continuous data. Analysis of Receiver operator characteristic (ROC) was performed to determine the optimal cut off value, the sensitivity, specificity, PPV, NPV and accuracy were calculated. For all tests P values were two-tailed and P-value <0.05 was considered statistically significant.

RESULTS:

21 patients (13 females and 8 males) were included in this study. Their ages ranged from 1 – 68 years.

Histopathological analysis and MRI features revealed that 10 and 11 of the orbital lesions in this study were benign and malignant respectively.

The benign lesions comprised 3 histocytosis (30%), 2 pseudotumor (20%), 2 cellulitis (20%), 1 cavernous hemangioma (10%), 1 capillary hemangioma (10%) and 1 lacrimal pleomorphic adenoma (10%) (Diagram 1).

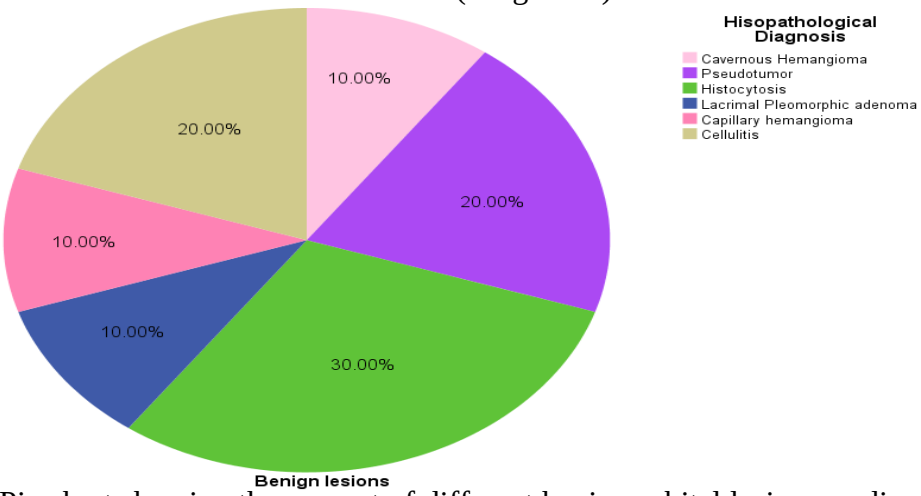

Diagram (1): Pie chart showing the percent of different benign orbital lesions as diagnosed by histopathology and/or MRI features.

The malignant lesions comprised 3 optic nerve gliomas (27.3%), 3 lymphomas (27.3%), 2 metastases (from breast cancer and neuroblastoma) (18.2%), 1 melanoma (9.1%), 1 rhabdiomyosarcoma (9.1%) and 1 retinoblastoma (9.1%) (Diagram 2).

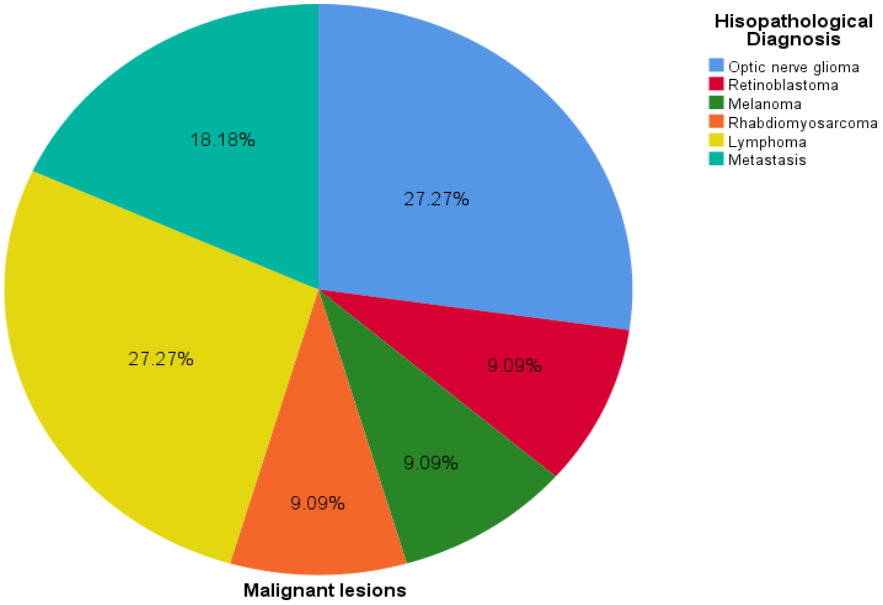

Diagram (2): Pie chart showing the percent of different malignant orbital masses as diagnosed by histopathology.

There was significant association between lesional signal intensity on DWI, ADC map and nature of the orbital lesions; the majority of malignant orbital lesions (54.5 %) were hyper intense as opposed to 90 % of benign lesions which were hypointense on DWI, with a significant difference between benign and malignant lesions (*p-value* = 0.001). The majority of malignant orbital lesions (63.6 %) were hypo intense on ADC as opposed to 70 % of the benign lesions which were hyperintense on ADC with a significant difference between benign and malignant lesions (*p-value* = 0.002) (Table 1).

Table (1): DWI signal intensity and ADC signal intensity among benign and malignant orbital lesions

	Benign	Malignant	P value	Sig
No of lesions	10 (47.6%)	11 (52.4%)		
SI in DWI			0.001*	S
Hypointense	9 (90%)	2 (18.2%)		
Isointense	1 (10%)	3 (27.3%)		
Hyperintense	0 (0%)	6 (54.5%)		
SI in ADC			0.002*	S
Hypointense	0 (0%)	7 (63.6%)		
Isointense	3 (30%)	3 (27.3%)		
Hyperintense	7 (70%)	1 (9.1%)		

* Fisher's Exact Test

When the orbital lesions were categorized as benign or malignant, both groups could be differentiated using mean ADC values. Benign tumors showed statistically significantly higher mean ADC values with (P < 0.001) (Table 2).

Table (2): Mean ADC values for benign and malignant groups. Data are expressed in median, interquartile range and range

ADC	Benign	Malignant	P value
Mean (± SD)	1.31 (±0.100)	0.82 (±224)	
Median	1.33	0.72	
Range	1.20 – 1.49	0.60 – 1.21	P < 0.001
IQR	1.20 – 1.39	0.63 – 1.08	

Using an ADC cut-off value of ≤1.145; 10 out of 11 malignant lesions were correctly classified as malignant (TP) while only one lesion (Optic Nerve Glioma) had an ADC of more than 1.145; (1.21) and was incorrectly classified as benign (FN). All of the 10 benign lesions had ADC values that were more than 1.145 and were correctly classified as benign (TN). No benign lesions had an ADC value of less than or equal 1.145; no (FP).

The ADC values of benign and malignant subgroups in this study could not be compared owing to the small sample size of the individual subgroups, however the ADC values of all benign and malignant lesions can be seen in (Table 3).

Table (3): Descriptive data of ADC value among all different benign and malignant orbital lesions in this study

	Mean	SD	Median	Max	Min	IQR	25^{th}	75^{th}
Optic nerve glioma	1.13	0.07	1.09	1.21	1.08	0.13	1.08	1.21
Retinoblastoma	0.64	-	0.64	0.64	0.64	0	.64	.64
Melanoma	0.74	-	0.74	0.74	0.74	0	.74	.74
Rhabdiomyosarcoma	0.98	-	0.98	0.98	0.98	0	.98	.98
Lymphoma	0.62	0.02	0.63	0.63	0.60	0.03	.60	.63
Metastasis	0.71	0.02	0.71	0.72	0.69	0.03	.69	.72
Cavernous Hemangioma	1.34	-	1.34	1.34	1.34	0	1.34	1.34
Pseudotumor	1.44	0.07	1.44	1.49	1.39	0.1	1.39	1.49
Histocytosis	1.21	0.02	1.20	1.24	1.20	0.04	1.20	1.24
Lacrimal Pleomorphic adenoma	1.40	-	1.40	1.40	1.40	0	1.40	1.40
Capillary hemangioma	1.33	-	1.33	1.33	1.33	0	1.33	1.33
Cellulitis	1.27	0.10	1.27	1.34	1.20	0.14	1.20	1.34

The lowest ADC values were seen in cases of lymphoma with a mean ADC (± standard deviation) of 0.62 (±0.02) $x10^{-3}mm^2/s$ and in metastasis where the mean ADC (± standard deviation) was 0.71 (±0.02) $x10^{-3}mm^2/s$. The highest ADC values were in cases of pseudotumor with a mean ADC (± standard deviation) of 1.44 (±0.07) $x10^{-3}mm^2/s$

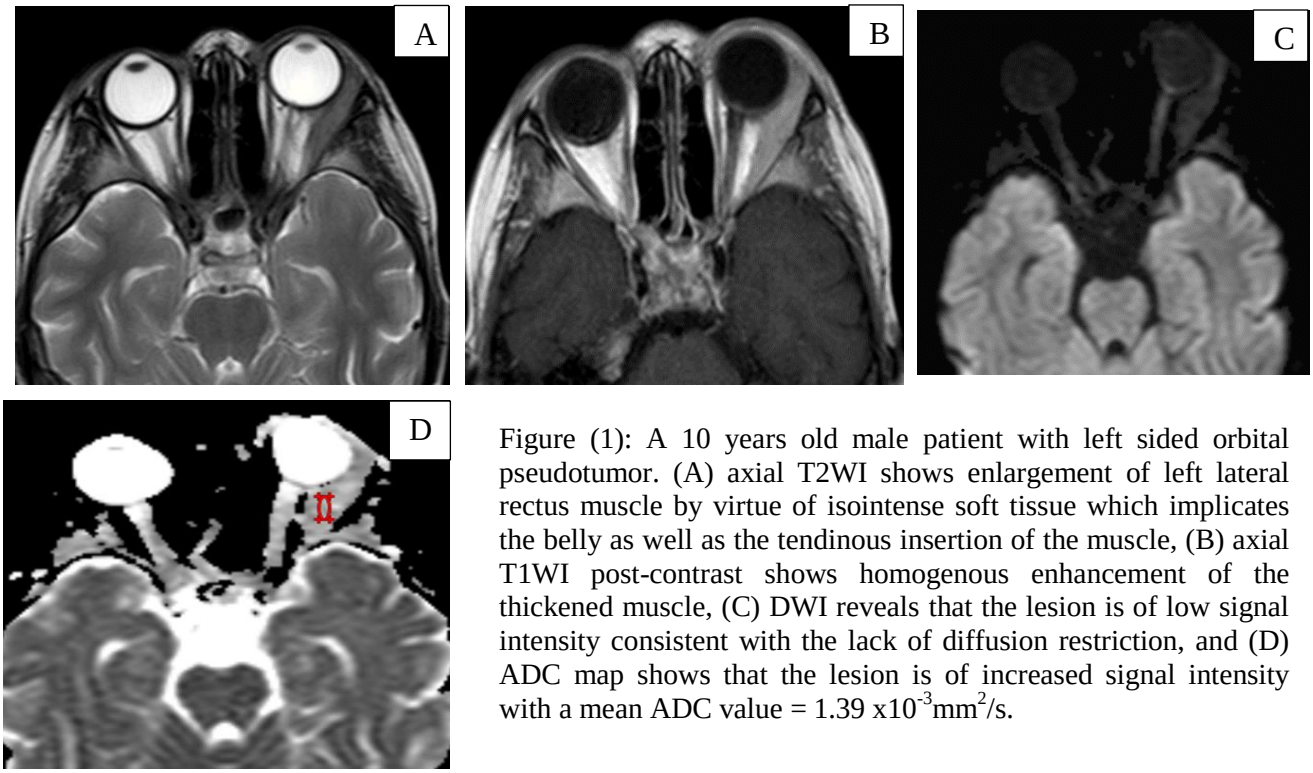

Figure (1): A 10 years old male patient with left sided orbital pseudotumor. (A) axial T2WI shows enlargement of left lateral rectus muscle by virtue of isointense soft tissue which implicates the belly as well as the tendinous insertion of the muscle, (B) axial T1WI post-contrast shows homogenous enhancement of the thickened muscle, (C) DWI reveals that the lesion is of low signal intensity consistent with the lack of diffusion restriction, and (D) ADC map shows that the lesion is of increased signal intensity with a mean ADC value = 1.39 $x10^{-3}mm^2/s$.

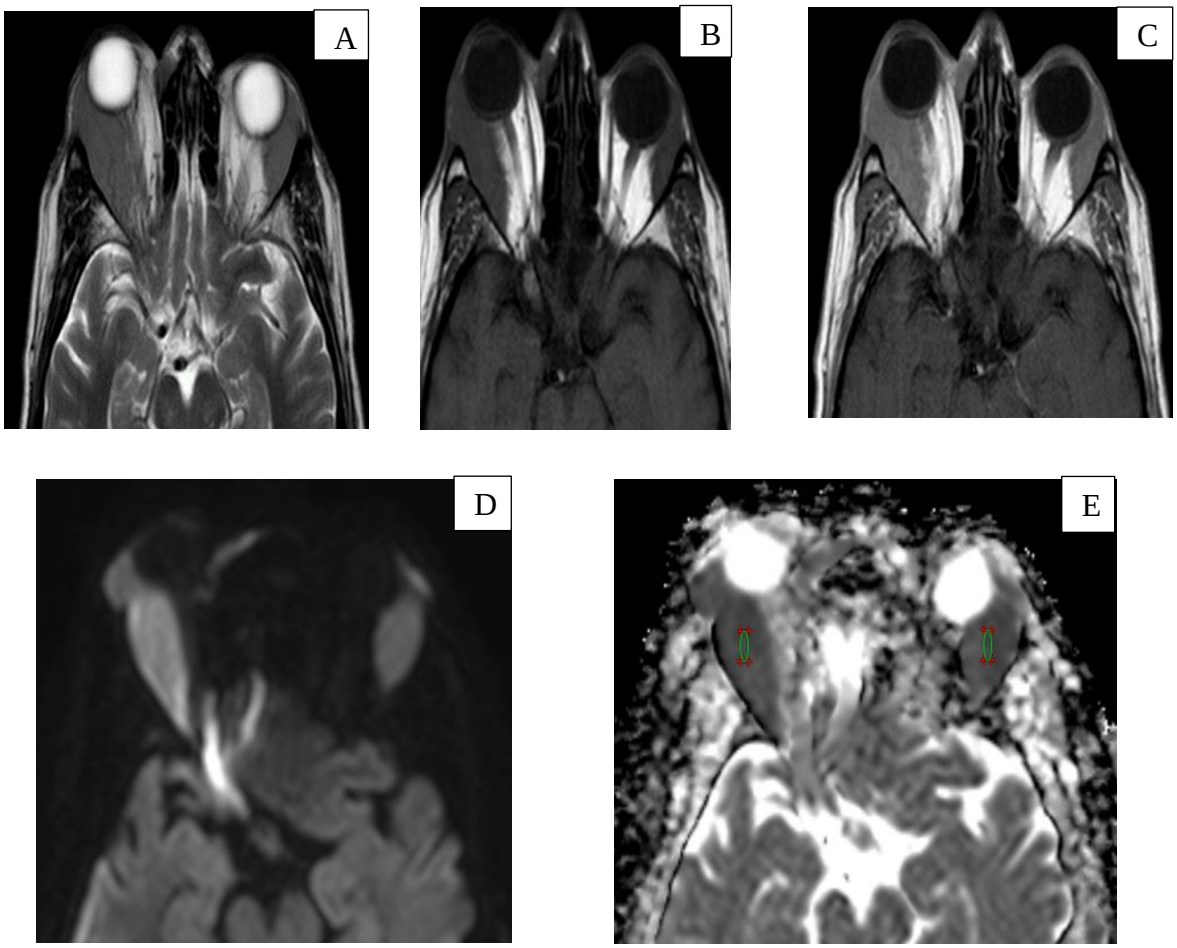

Figure (2): A 17 years old male patient with bilateral orbital lymphoma. (A) Axial T2WI and (B) axial non-contrast T1WI show iso to hypointense soft tissue masses involving both lacrimal glands and extending posteriorly into the orbit more on the right side. (C) axial T1WI post-contrast shows homogenous enhancement of the orbital masses, (D) DWI and (E) ADC map confirm the restricted diffusion of the masses as denoted by the increased signal on DWI and the homogenously low signal on the corresponding ADC map with a mean ADC value= 0.63 $x10^{-3}mm^2/s$ consistent with the well-documented dense cell packing of lymphomas, a diagnosis which was verified by histopathology.

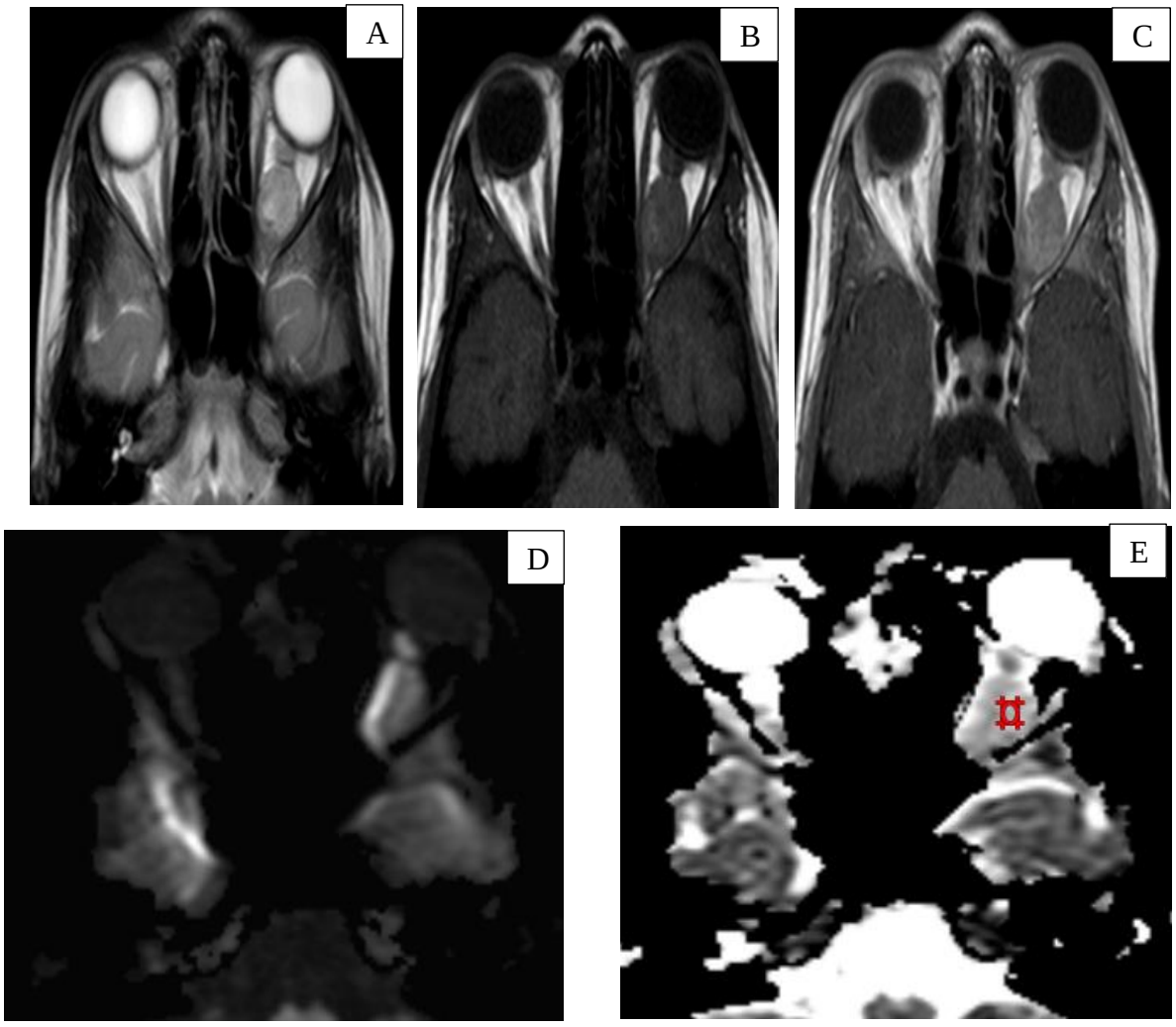

Figure (3): A 10 years old female patient with histologically proven left optic nerve glioma. (A) axial T2WI shows a hyperintense well defined mass of left optic nerve, (B) axial non-contrast T1WI shows an isointense mass of the left optic nerve (C) axial T1WI post-contrast shows mild hetrogenous enhancement of the mass, (D) DWI and (E) ADC map display facilitated diffusion within the mass as denoted by the increased signal intensity of the mass on both DWI and ADC with a mean ADC value = 1.21 $x10^{-3}mm^2/s$. Despite being malignant, optic nerve gliomas are known to be low grade lesions with low cellularity which is responsible for the confounding results on diffusion imaging. The increased signal intensity of the lesion on DWI is likely attributed to the T2 shine through effect.

DISCUSSION:

Using magnetic resonance imaging (MRI), some lesions can be diagnosed easily depending on the imaging findings such as typical location and enhancement pattern, but for lesions without these pathognomonic characteristics, their characterization as inflammatory, benign or malignant orbital masses may be difficult. (5)

Diffusion-weighted imaging is a modality that makes use of magnetic resonance (MR) imaging to depict the diffusivity of water molecules in a defined voxel by means of the application of motion-probing gradients. This imaging property is unique and provides a different contrast mechanism than that observed on conventional T1- and T2- weighted MR images. In addition, the analysis of apparent

diffusion coefficient (ADC) value can be undertaken.[6]

Restriction in the diffusion of water molecules (high signal in DWI and low signal in ADC) is directly proportional to the degree of cellularity of the tissue. This restricted diffusion is observed primarily in malignancies, hypercellular metastases, and fibrosis. In contrast, in a microenvironment with fewer cells and a defective cell membrane, water molecules are able to move freely (i.e. diffusion is less restricted).[7]

Our study supported the fact mentioned above by revealing a significant association between signal intensity of lesions on the ADC map and nature of the orbital lesions as confirmed by histopathological analysis, where the majority of malignant orbital lesions (63.6 %) were hypointense on ADC as opposed to 70% of the benign lesions which appeared hyperintense on ADC with significant difference between benign and malignant lesions (p-value = 0.002). This was in agreement with ***Fatima et al*** [8]who reported that the signal characteristics on ADC maps (hyperintensity: hypointensity, 17:4 in benign lesions and 3:15 in malignant lesions; p-value ≤ 0.0001) with significantly different in benign vs. malignant lesions.

Similar to ***Roshdy et al*** [9] who reported that on DWIs, (50%) of benign lesions appeared hypo intense "free diffusion" and all (100%) malignant tumors appeared hyper intense "restricted diffusion", this study revealed that 54.5% and 90% of malignant and benign orbital lesion appeared hyperintense and hypointense on DWI respectively with significant difference between benign and malignant lesions (p-value = 0.001). However, caution must be exercised during assessment of DW images as the signal intensity on DWI can be affected by both the diffusivity of the tissue and the T2 relaxation; the so-called T2 shine through effect, which explains why ***Fatima et al*** [8]reported that visual assessment of DWI images did not reveal a significant difference (hyperintensity: hypointensity, 17:4 in benign lesions and 16:2 in malignant lesions; p-value = 0.66) between benign and malignant lesions.

Several older studies demonstrated that malignant masses have significantly lower ADC values than benign lesions. ***Abdel Razek et al*** [4] reported that the mean ADC value for malignant masses was 0.8 ± 0.34 $x10^{-3}mm^2/s$, and for benign lesions it was 1.53 ± 0.35 $x10^{-3}mm^2/s$ with a significant difference (P=0.001). ***Fatima et al*** [8] reported that the mean ADC value for malignant masses was 0.77 ± 0.38 $x10^{-3}mm^2/s$, and for benign lesions it was1.23 ± 0.42 $x10^{-3}mm^2/s$. ***Sepahdari et al*** [10] reported that the mean ADC value for malignant masses was 1.02 ± 0.42 $x10^{-3}mm^2/s$, and for benign lesions it was 1.36 ± 0.41 $x10^{-3}mm^2/s$ with a significant difference between both groups (P=0.0001). ***Hemat*** [5] found that the mean ± SD for ADC values in malignant and benign orbital masses was 0.77 ± 0.22 $x10^{-3}mm^2/s$ and 1.41 ± 0.38 $x10^{-3}mm^2/s$ respectively revealing a significant difference (p-value < 0.001). Consistently the mean ADC value for malignant orbital masses in this study was 0.82 ±0.224 $x10^{-3}mm^2/s$ (range 0.60 – 1.21 $x10^{-3}mm^2/s$) while for benign lesions it was 1.31 ±0.1 $x10^{-3}mm^2/s$ (range 1.20 – 1.49 $x10^{-3}mm^2/s$) with significant difference between benign and malignant lesions (p-value < 0.001). The reason for this behavior is thought to be because of the peculiar enlarged and deformed nuclei and hypercellularity characteristics of malignant lesions, thus reducing the available diffusion space for water protons in both the extracellular and intracellular spaces.[8]

In this study, an ADC cut-off value of ≤1.145 $x10^{-3}mm^2/s$ could differentiate malignant tumors from benign lesions with a sensitivity of 90.9%, a specificity of 100% and an accuracy of 95.2%.

Similarily ***Abdel-Razek et al*** [4] found using an ADC cut-off value of 1.15 $x10^{-3}mm^2/s$ yielded a sensitivity of 95%, specificity of 91% and accuracy of 93 % in differentiation of malignant and benign lesions. ***Fatima et al*** [8]however, used a lower ADC cutoff value of 0.84 $x10^{-3}mm^2/s$ and this resulted in 83.33% sensitivity and 85.71% specificity for distinguishing malignant from benign lesions. ***Hemat*** [5] found that by using ADC cutoff value of 0.93 $x10^{-3}mm^2/s$ the sensitivity was 80%, the specificity was 83.3% and the accuracy was 82%.

ADC has important role in different clinical orbital problems that affect patient management, for example in differentiating orbital lymphoma from pseudotumor that may simulated in clinical presentation and MR imaging appearance. Prompt early diagnosis is needed as the management differs greatly.[4] The ADC values of benign and malignant subgroups in this study could not be compared owing to the small sample size, however the results of this study showed that the ADC values of lymphomas were markedly lower than those of pseudotumor with no overlap found between their ADC values. The high cellularity and enlarged nuclei of orbital lymphoma leads to relative reduction in extracellular and intracellular diffusion spaces with a resultant decrease in the ADC value. The low mean ADC value of 0.62 $x10^{-3}mm^2/s$ (range 0.60 - 0.63 $x10^{-3}mm^2/s$) of lymphomas in this study was comparable to values published by previous studies including mean ADC value of $0.67x10^{3}mm^2/s$ reported by ***Abdel-Razek et al*** [4], and by ***Sepahdari et al*** [10], ***and*** 0.61 $x10^{-3}mm^2/s$ reported by ***Fatima et al*** [4].

On the other hand, interstitial edematous change in idiopathic orbital inflammatory pseuotumor gives rise to increase ADC, promoting a significant difference in the ADC value than lymphoma. This explains the high mean ADC value of 1.44 (±0.07) $x10^{-3}mm^2/s$ (range 1.39 – 1.49 $x10^{-3}mm^2/s$) of psuedotumor in this study which was comparable to values published by previous studies including mean ADC value of 1.40 (0.31) $x10^{-3}mm^2/s$ reported by ***Sepahdari et al*** [10], and 1.57 (± 0.38) $x10^{-3}mm^2/s$ (range 1.1 – 2.2 $x10^{-3}mm^2/s$) reported by ***Hemat*** [5]**.**

In agreement with ***Abdel-Razek et al*** [4] and ***Hemat*** [5] who found that the mean ADC value of metastasis was significantly higher than that of lymphoma, the mean ADC value of metastasis in this study (0.71 $x10^{-3}mm^2/s$, range:0.69 – 0.72 $x10^{-3}mm^2/s$) was higher than lymphoma with no overlap among their individual values. ***Hemat*** [5]explained this by the fact that lymphoma has high cellularity which even exceeds the high cellularity of other malignant tumors. Nevertheless, the mean ADC value for metastasis in this study was lower than the mean ADC values of 0.98 $x10^{-3}mm^2/s$ and 1.04 $x10^{-3}mm^2/s$ reported by ***Abdel-Razek et al*** [4] and ***Hemat*** [5] respectively for metastasis. This difference could be attributed partly to the limited number and variety of metastases included in this study.

A single optic nerve glioma with a high ADC value of 1.21 $x10^{-3}mm^2/s$ was misdiagnosed as a benign tumor, thus constituting the single false negative result in this study. The low cellularity and proliferative index of optic nerve gliomas as well as being low grade tumors classified histologically as pilocystic astrocytomas, is thought to explain their high ADC values. Similar observations were made by ***Fatima et al*** [8] and ***Hemat*** [5]**.**

The limitations of this study included the limited number of cases enrolled in the study and the small sample size of each subgroup which could have affected the accuracy of our results. Histopathological analysis was not available for some of the benign lesions, so the final diagnosis of

these cases was based upon clinical history, imaging appearance and time - interval follow. There may be some bias from selection of the region of interest to calculate the ADC value. We tried to overcome this problem with the careful positioning of the ROIs to include only solid, non-necrotic, non-cystic, non-calcified and non-hemorrhagic tumors' parts for the ROI-based analysis.

Conclusion:

DWI and ADC maps with ADC value calculations are useful for differentiating between malignant and benign orbital tumors. Apparent diffusion coefficient value can solve some clinical problems of the orbit that affect patient management.

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أهمية الرنين المغناطيسي (خاصية الانتشار و معامل الانتشار الظاهري) في التمييز بين آفات الحجاج الحميدة و الخبيثة

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قسم الأشعة التشخيصية ، كلية الطب ، جامعة عين شمس، *المعهد القومي لأبحاث الأمراض المتوطنة والكبد بالقاهرة

المقدمة: تعد تكتلات الحجاج و تكتلات داخل العين غير مشهورة نسبيا بالمقارنة بالآفات التكتلية الأخري بالجسم حيث تم وصف أن ثلثي أورام الحجاج حميدة و ثلثها خبيثة. وقد يكون من الصعب التمييز بين هذة الأسباب مستندا علي النتائج الاكلينيكية. قد يساعد الرنين المغناطيسي في وصف تكتلات الحجاج المختلفة لأن بعضها له صفات خاصة المعتاد ولكن في الأغلب يصعب التمييزبين هذة الصفات. يعد التصوير بخاصية الانتشارمعتمدا علي الرنين المغناطيسي تقنية حديثة حيث له القدرة علي توصيف و تمييز الخصائص المورفولوجية من خلال قياس الاختلافات في معامل الانتشار الظاهري التغيرات وبذلك تساعد في التمييز بين آفات الحجاج الخبيثة و الحميدة والتي هي محور التخطيط في علاج المريض.

الهدف من الدراسة: هو البحث في فائدة تصوير الرنين المغناطيسي بخاصية الأنتشار و القيم الناتجة من معامل الأنتشار الظاهري في التمييز بين التكتلات الحميدة و الخبيثة بالحجاج.

المرضي و طرق البحث: اشتملت هذة الدراسة علي ٢١ مريض (١٣ اناث و ٨ ذكور) يعانون من وجود تكتلات بالحجاج و ذلك مثبت من خلال فحص أشعة متاح.

النتائج: من بين واحد و عشرين مريض وجد أحد عشر حالة يعانون من أورام خبيثة بالحجاج و عشر حالات لديهم تكتلات حميدة ،بواقع عشرة من أصل أحد عشر حالة ايجابية مثبتة بوجود ورم خبيث و جميع الحالات العشرة الأخري مثبت لديها وجود تكتلات حميدة بنسبة دقة تصل الي ٩٠.٩ % و نسبة تشخيص عالية تصل الي ١٠٠%.

الخلاصة: هناك أهمية كبيرة لخاصية الانتشار و خرائط معامل الانتشار الظاهري و قيمها في التمييز بين أورام الحجاج الخبيثة و الحميدة. كما أن قيم معامل الانتشار الظاهري تحل الكثير من المشاكل الاكلينيكية في الحجاج و التي تؤثر في خطة علاج المريض.