Role of diffusion-weighted magnetic resonance imaging in evaluation of chronic kidney disease

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Objective
The aim was to assess diffusion-weighted magnetic resonance imaging (DW-MRI) and apparent diffusion coefficient (ADC) of the renal parenchyma role in evaluation of different chronic kidney disease stages.

Introduction
MRI has a special ability to evaluate both renal structure and function objectively without any radiation hazards.

Patients and methods
This study enrolled 38 patients with chronic kidney disease (CKD) and 30 participants as healthy volunteers (sex and age matched). Abdominal MRIs with DWI results were compared with the level of estimated glomerular filtration rate.

Results
There were no significant differences in the ADC values of our studied patients between the right and left kidneys or between male and female. The entire control group had facilitated diffusion, whereas 70 and 30% patients with CKD had facilitated and restricted diffusion, respectively. Patients with CKD had significantly lower ADC in comparison with control group. The mean ADC was significantly decreasing with advancing stage of CKD, where stage I CKD had the highest mean ADC, whereas stage V CKD had lowest mean ADC. The ADC had a negative weak correlation with serum creatinine ($r = -0.30$; $P = 0.04$) but a positive moderate correlation with creatinine clearance ($r = 0.56$; $P = 0.01$).

Conclusion
The renal ADC had 86% sensitivity and 100% specificity in diagnosing chronic kidney disease, so the authors can depend on DWI and ADC in diagnosis and differentiating CKD stages.

Keywords:
apparent diffusion coefficient, chronic kidney disease, diffusion-weighted imaging

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Introduction

Chronic kidney disease (CKD) is a common worldwide public health problem, which continues to inexorably rise. CKD mortality has increased by 31.7% over the past 10 years [1]. As renal parenchymal disease is associated with renal dysfunction, renal function monitoring allows assessment of disease progression. Although blood urea, serum creatinine, and estimated glomerular filtration rate (eGFR) derived from creatinine clearance are helpful for renal function monitoring, they are imperfect and cannot assess the functions of a single kidney [2].

Different imaging modalities play an impressive role in assessment of renal parenchymal disease. Ultrasonography and computed tomographic (CT) scan give good anatomic details but limited physiological information. Although ultrasonography may show changes in renal echogenicity, it is operator dependent. Besides the exposure to ionizing radiation, CT scan requires use of iodinated contrast material, which is nonpreferable in patients with renal dysfunction [3].

Diffusion-weighted MRI (DW-MRI) is a noninvasive imaging modality that can characterize tissues based on Brownian motion of water molecules. apparent diffusion coefficient (ADC) is a quantitative parameter calculated from DWI, which combines the effects of water diffusion and capillary perfusion. DW-MRI in renal diseases is a developing field, and many attempts have been made to assess its role in the characterization of renal parenchymal disease, renal infections, and focal renal lesions [4].

Aim

The aim was to assess the role of DW-MRI and ADC of the renal parenchyma in evaluation of different stages of chronic kidney disease and their relationship with serum markers of renal function.

Patients and methods

Our study was conducted at the radiology department of Assiut University Hospital between October 2017 and November 2018 and was registered with clinicalTrials.gov ID NCT03174899. This was a cross-sectional observational study and enrolled 38 patients with CKD, where three of them had a single kidney, so the total number of the diseased kidneys was 73. Moreover, 30 participants with 60 kidneys were enrolled as healthy volunteers (age and sex matched, with $P > 0.05$). Mean age of the study group was 54.89 ± 17.42 years, and it comprised 55.3% female patients. However, the mean age of control group was 45.26 ± 18.25 years, and it comprised 53.3% female participants. Our study was approved by the Local Ethical Committee, IRB#17100218, and written informed consent was taken from all patients. We excluded from our study patients who had any general contraindication to MRI, such as presence of a paramagnetic substance, for example, pacemakers; those with claustrophobia or severely ill patients; patients with CKD of postrenal etiology (e.g. hydronephrosis); patients who had an acute kidney injury; and those with renal tumors.

All participants were subjected to the following:

(1) Detailed information from patients regarding age, weight, sex, diabetes mellitus, hypertension, infection, and AKI.
A blood sample was collected to measure the serum creatinine for estimation of GFR to determine CKD stage by the Chronic Kidney Disease Epidemiology Collaboration (CDK-EPI) equation expressed as a single equation, as follows: GFR = 141 × min (SCr/κ,1) α×max (SCr/κ,1)−1.209 × 0.993Age × 1.018 [if female]×1.159 [if black] (measured in ml/min/1.73 m^2) [5].

(2) Abdominal MRI was obtained for both groups using a 1.5-T scanner (Acheiva,Philips Netherlands).The patient was placed in the supine position using eight-channel body coil.

MR imaging

Axial DW multisection echo-planar MRI was performed with diffusion gradient *b* values of 0–800 s/mm^2. The following parameters were used for this sequence: echo time 70, repetition time 1535, gap 1 mm, slice thickness 7 mm, field of view 435 × 350 mm, reconstruction matrix size 224, and flip angle 90°.

A region of interest (ROI) was placed in the axial ADC map for measurement of ADC values on renal parenchyma bilaterally, without any preference for cortex or medulla. Three circular ROIs of size 1 cm^2 were placed at the upper pole, middle polar region, and lower pole of both kidneys, and 6 total ROIs from both kidneys were averaged for each patient. The mean ADC values for each patient were recorded, and the relationship of ADC values and CKD stage was assessed. All sequences were performed during a single breath-hold.

Statistical analysis

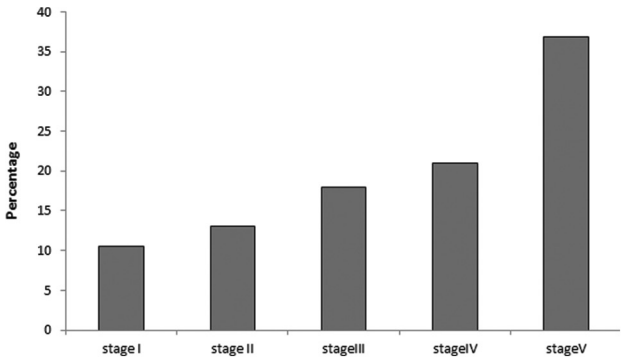
The data were collected and analyzed using SPSS (Statistical Package for the Social Sciences, version 20; IBM, Armonk, New York, USA). Continuous data were expressed in the form of mean ± SD or median (range), whereas nominal data were expressed in the form of frequency (percentage). χ^2-test was used to compare the nominal data of different groups in the study, whereas Student's *t*-test was used to compare means of two different groups and analysis of variance test for more than two groups. Spearman correlation was used to determine the correlation between ADC with serum creatinine and creatinine clearance. Diagnostic performance of ADC and restricted diffusion in diagnosing CKD was determined by using ROC curve. Confidence level was kept at 95%, and hence, *P* value was considered significant if less than 0.05.

Results

Overall, four (10.5%), five (13.2%), seven (18.4%), eight (21.1%), and 14 (36.8%) patients had CKD stages I, II, III, IV, and V, respectively. A total of five (13.2%) patients were on regular dialysis, whereas 33 (86.8%) patients did not need dialysis, as shown in Fig. 1.

All healthy volunteers had facilitated diffusion, whereas among the patients with CKD, 51 (70%) had facilitated and 22 (30%) had restricted diffusion. Patients with CKD had significantly lower ADC in comparison with healthy volunteers. The mean ADC

Figure 1



Laboratory stages of chronic kidney disease in studied patients.

was 1.73 ± 0.17 × 10^{-3} mm^2/s in case of patients with CKD, and it was 2.06 ± 0.12 × $10^{-3}mm^2/s$ in case of healthy volunteers, as shown in Table 1.

There was no significant ADC value difference between right and left kidney or between male and female sex, with *P* greater than 0.05.

ADC had a negative weak correlation with serum creatinine (r = −0.30; P = 0.04) and a positive moderate correlation with creatinine clearance (eGFR) (r = 0.56; P = 0.01), but it had an insignificant weak correlation with age (r = −0.14; P = 0.07), as shown by Figs. 2 and 3.

Mean ADC was significantly decreasing with higher stages of CKD, where stage I CKD had highest mean ADC (2.01 ± 0.10 × 10^{-3} mm^2/s), whereas stage V CKD had lowest mean ADC (1.53 ± 0.15 × 10^{-3} mm^2/s), as shown in Table 2 and Figs. 4 and 5.

Diagnostic performance of renal ADC in diagnosing CKD

At a cutoff point less than 1.91 × $10^{-3}mm/s$, renal ADC had 86% sensitivity and 100% specificity in diagnosing CKD, with area under curve (AUC) of 0.95 and *P* less than 0.001, as shown in Fig. 6.

Diagnostic performance of restricted diffusion in diagnosing CKD

Restricted diffusion had 31% sensitivity and 100% specificity in diagnosing CKD, with AUC of 0.65 and *P* value of 0.04, as shown in Fig. 7.

Table 1 Diffusion and apparent diffusion coefficient data of the studied kidneys

	Study group (*n*=73)	Control group (*n*=60)	*P*
Diffusion			0.03
Facilitated	51 (70)	60 (100)	
Restricted	22 (30)	0	
ADC (×10^{-3}mm/s)			
Right kidney	1.74±0.16	2.05±0.12	<0.001
Left kidney	1.74±0.20	2.07±0.12	<0.001
Mean	1.73 ± 0.17	2.06 ± 0.12	<0.001

With exclusion of three kidneys. Data are showed in the form of frequency (percentage), mean±SD). ADC, apparent diffusion coefficient.

Table 2 Apparent diffusion coefficient in patients based on stages of chronic kidney disease

Stages of CKD	Mean±SD (×10^{-3} mm^2/s)
Stage I	2.01±0.10
Stage II	1.89±0.10
Stage III	1.74±0.11
Stage IV	1.68±0.17
Stage V	1.53±0.15
P	0.03

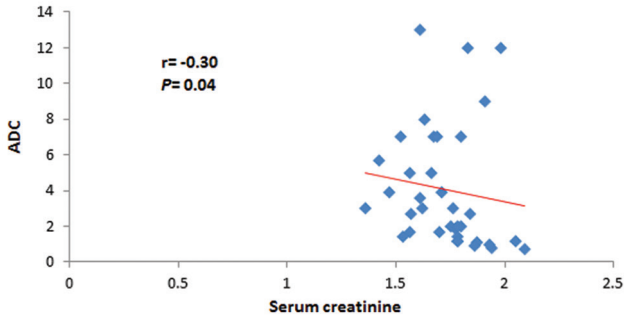
Data are shown in the form of mean±SD. CKD, chronic kidney disease.

Discussion

Abdominal DW-MRI using a single breath-hold technique gives us images with high quality [6] and has been used in previous studies, such as Yoshikawa and colleagues, Murtz and colleagues, Flacke and colleagues, Xu and colleagues, and Chow and colleagues [6–9]

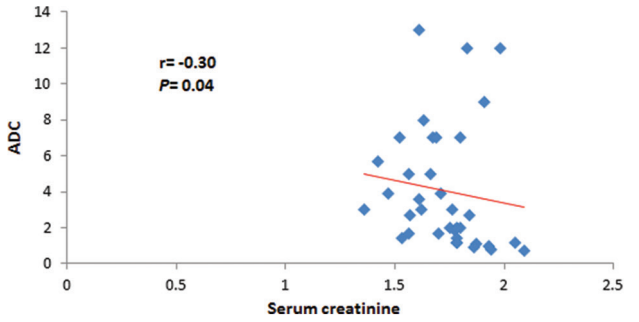
Some investigators such as Mürtz and colleagues, Thoeny and colleagues, and Yoshikawa and colleagues [7,8,10] used *b* value larger than 400 s/mm^2

Figure 2



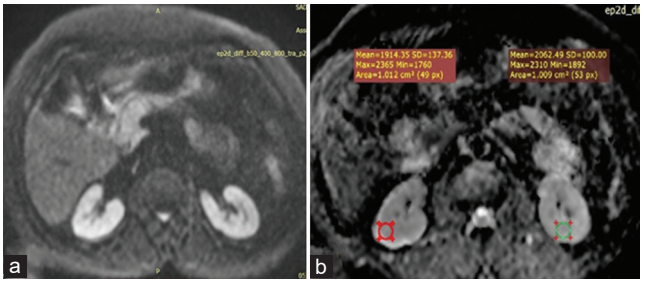
Apparent diffusion coefficient and serum creatinine correlation.

Figure 3



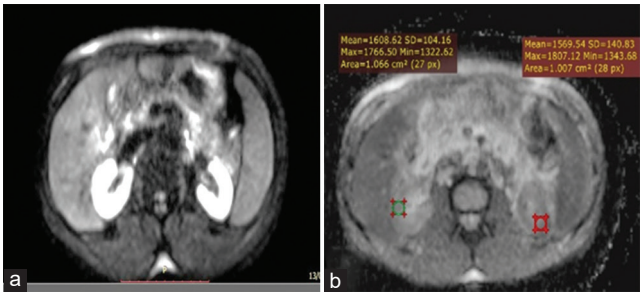
Apparent diffusion coefficient and creatinine clearance (estimated glomerular filtration rate) correlation.

Figure 4



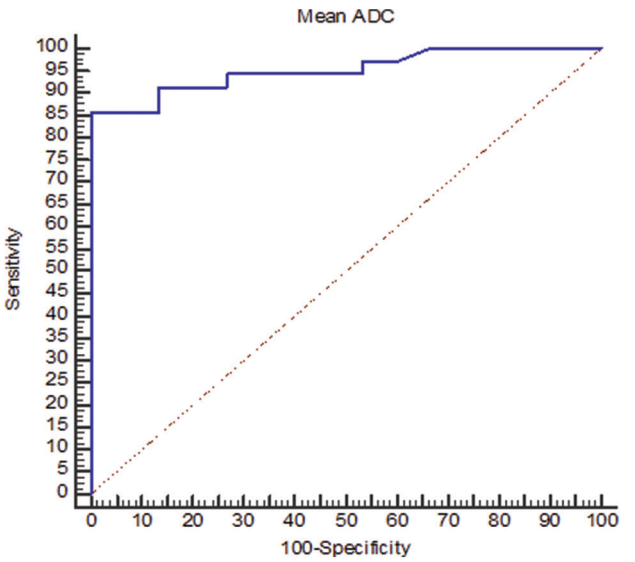
A 56-year-old male known to be diabetic and hypertensive. On laboratory evaluation, his serum creatinine was 0.8 mg/dl, estimated glomerular filtration rate was 100 ml/min, and was diagnosed as chronic kidney disease stage I. (a) Axial DWI revealed low signal intensity of both kidneys at b value 800. (b) The mean apparent diffusion coefficient value on the right side was 1.9 × 10^{-3} mm^2/s and on the left side was 1.9 × $10^{-3}mm^2/s$.

Figure 5



A 26-year-old male not known to be diabetic or hypertensive. On laboratory evaluation, his serum creatinine was 13 mg/dl, estimated glomerular filtration rate was 5 ml/min, and was diagnosed as chronic kidney disease stage 5. (a) Axial DWI revealed global high signal intensity involving both kidneys at *b* value 800. (b) The mean apparent diffusion coefficient value on the right side was 1.6 × 10^{-3} mm^2/s and on the left side was 1.5 × $10^{-3}$$mm^2$/s.

Figure 6



Diagnostic performance of renal apparent diffusion coefficient in diagnosing chronic kidney disease.

to minimize the effects of intravoxel perfusion and T2 shine-through. To maintain SNR, we set the *b* values at 0 – 400 and 800 s/mm^2, and this was consistent with most previous studies such as Squillaci *et al.*, Thoeny *et al.*, and Xu *et al.* [9–11].

Based on laboratory investigation (eGFR evaluation) of our studied patients, most of our cases were CKD stages IV [8 (21.1%)] and V [14 (36.8%)]. This was different from the study by Yalçin-Şafak *et al.* [12], in which stages II [33 (30.0%)] and III [43 (39.1%)] had the highest percentage. This was attributed to their retrospective study, which included all patients who underwent MRI abdomen for different reasons other than CKD between September 2014 and February 2015 (wide base selection).

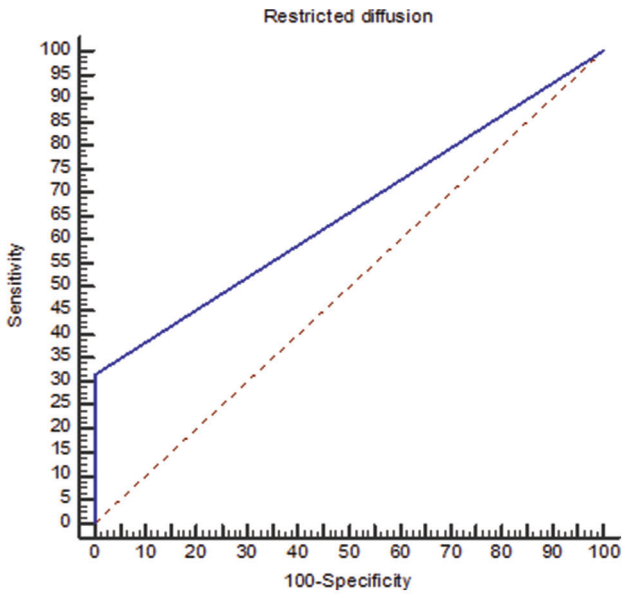
It was noticed that all our healthy volunteers had facilitated diffusion, whereas 51 (70%) and 22 (30%) patients with CKD had facilitated and restricted diffusion, respectively. This is consistent with Namimoto *et al.* [13], who reported that there was a slight decrease in the signal intensity in CRF kidneys compared with that in the normal kidneys, which was attributed to the restriction of molecule motion that resulted from reduction of water transport functions and the fibrosis in CRF kidneys.

No significant differences were found in the values of ADC of our studied patients between the left and right kidneys (1.74 ± 0.16 × 10^{-3} and 1.74 ± 0.20 × $10^{-3}$$mm^2$/s, respectively; P = 0.08) and the same was found in the control group with ADC values of 2.05 ± 0.12 × 10^{-3} and 2.07 ± 0.12 × $10^{-3}$$mm^2$/s, respectively; P = 0.109). Moreover, no significant difference in the renal ADC values between male and female patients was found in the studied patients (1.76 ± 0.19 × 10^{-3} and 1.70 ± 0.14 × $10^{-3}$$mm^2$/s, respectively; P = 0.3). This was consistent with Xu *et al.* [4], where ADC values were 2.37 ± 0.31 × 10^{-3} and 2.40 ± 0.34 × $10^{-3}$$mm^2$/s. This may be attributed to that most of CKD causes were owing to systemic diseases. Moreover, we found an insignificant weak correlation between the ADCs and the age of the patients. This was in disagreement with Xu *et al.* [4], who reported that there was anticorrelation between the age of the patients and their ADC values.

We found an inverse relationship of ADCs and SCr (r = –0.30; P = 0.04). This was consistent with Yalçin-Şafak *et al.* [12], who reported that there were significantly inverse correlations between ADC values and serum creatinine values (r = –0.316; P = 0.001), and also with Xu *et al.* [4] (r = –0.374, P = 0.000). We also found a direct moderate linear correlation with creatinine clearance (eGFR) (r = 0.56; P = 0.01).

We found that ADC values in patients with CKD were lower than that of non-diseased kidneys, as mean ADC was 1.73 ± 0.17 × $10^{-3}$$mm^2$/s in case of patients with CKD and it was 2.06 ± 0.12 × $10^{-3}$$mm^2$/s in case of healthy volunteers. This was consistent with several studies, such as Goyal *et al.* [14], who reported that values of ADC in patients with CKD were significantly lower than those who had normal renal function (2.1133 ± 0.2851 vs 2.3198 ± 0.1246 (×10^{-3} mm^2/s); Yoshikawa *et al.* [7], who reported that ADCs were significantly lower in patients had renal failure (right: 2.15 ± 0.30 × 10^{-3} mm^2/s and left: 2.11 ± 0.25 × 10^{-3} mm^2/s) than in those without disease (right: 2.67 ± 0.29 × 10^{-3} mm^2/s and left: 2.60 ± 0.32 × 10^{-3} mm^2/s) (P < 0.005); Yalçin-Şafak *et al.* [12], who found that ADC values of non-diseased participants were significantly higher than that

Figure 7



Diagnostic performance of restricted diffusion in diagnosing chronic kidney disease.

of patients with CKD; and also Xu *et al.* [4], who reported that patients with CKD except stage I had significantly lower renal ADC (t = −4.383, P = 0.000) than volunteers.

Previous studies such as Thoeny *et al.*, Toyoshima *et al.*, and Namimoto *et al.* [10,13,15] did not demonstrate differences in measurement of ADC values among the CKD different stages. We found in our study, a linear correlation between different CKD stages and renal ADC values. This was in consistent with Xu *et al.* [4] and Yalcin-Safak *et al.* [12]. We found in our study that the mean ADC values of different stages of CKD showed a decreasing trend with increasing stage and were significantly different from each other using b values ranging between 0 and 400 – 800 s/mm^2, as the mean ADC values for stage I was 2.01 ± 0.10 × 10^{-3} mm^2/s, stage II was 1.89 ± 0.10 × 10^{-3} mm^2/s, stage III was 1.74±0.11×10^{-3}mm^2/s, stage IV was 1.68±0.17×10^{-3}mm^2/s, and stage V was 1.53 ± 0.15 × 10^{-3} mm^2/s. This was similar to Yalçin-Şafak *et al.* [12], who found that the mean values of the ADC were different from each other and decreased with increasing the stage of CKD using b values from 0 to 400 s/mm^2, but with differences in ADC values, which were 1178.00 ± 50.39 × 10^{-3} mm^2/s) for stage I, 1198.94 ± 98.34 × 10^{-3} mm^2/s for stage II, 1139.16 ± 97.61 × 10^{-3} mm^2/s for stage III, 1021.00 ± 149.95 × 10^{-3} mm^2/s for stage IV, and 1009.38 ± 123.58 × 10^{-3} mm^2/s for stage V using b values of 0 and 400 s/mm^2. This is in agreement with Goyal *et al.* [14], who reported that ADC values were 2.2964 ± 0.1243 × 10^{-3} mm^2/s for stage III, 1.8413 ± 0.2117 × 10^{-3} mm^2/s for stage IV, and 1.5218 ± 0.1853 × 10^{-3} mm^2/s for stage V. However, they used b values from 0 to 500 s/mm^2 and patient with stages I and II CKD were not included in their study.

Finally, it was noticed that the renal ADC had 86% sensitivity and 100% specificity in diagnosing CKD, with AUC of 0.95 and P less than 0.001, whereas restricted diffusion had 31% sensitivity and 100% specificity in diagnosing CKD, with AUC of 0.65 and P of 0.04, and at cutoff point less than 1.91(×10-3mm^2/s). This was different from Yalcin-Safak *et al.* [12] as they had sensitivity of 75.44%, specificity of 69.81%, and AUC of 75.2%, and Goyal *et al.* [14], who obtained AUC of 0.720, ADC cutoff value of 2.2499 × 10^{-3} mm^2/s, sensitivity of 58.8%, specificity of 79.4%, and 95% confidence intervals of 0.562, 0.878. In addition, ADC values higher than 2.4516 × 10^{-3} mm^2/s were seen only with normal renal function (100% sensitivity) and lower than 2.0354 × 10^{-3} mm^2/s were seen only with renal dysfunction (100% specificity).

This means that ADC values were more sensitive in differentiating between different CKD stages than diffusion MRI; however, both are 100% specific in diagnosing CKD.

We faced the following potential limitations:

(1) The effect of hydration and dehydration on patients and volunteers was not evaluated.
(2) The correlation between renal histopathology and ADCs of patients and the effect of ascites on renal ADCs were not assessed.
(3) As we measured ADC values manually, it involved a degree of subjectivity. Therefore, automated ROI delineation methods that are more accurate are needed.

We recommended the following:

(1) Renal DW-MRI appears to be a reproducible and convenient noninvasive method for renal function evaluation, so we can use it in addition to existing kidney MRI protocols to detect the early stages of CKD.
(2) More studies are needed to validate our results and confirm this technique for clinical application.

Conclusion

There was a significant relationship between the ADC values and GFR, as the ADC values of CKD kidneys were significantly lower than normal kidneys, and the mean ADC values of different CKD stages were significantly different from each other and showed a decreasing trend with increasing stage. The renal ADC had 86% sensitivity and 100% specificity in diagnosing

chronic kidney disease, so we can depend on DWI and ADC in diagnosis and differentiating CKD stages. We hope that our research could decrease renal biopsy numbers used for renal affection diagnosis; however, it is still obscure whether the noticed decrease of ADC values mirrors the decrease of renal function only or the degree of tissue fibrotic changes or both.

Acknowledgements

Doaa M. Ahmed carried out the collection of patients, filled their complete clinical sheets, and performed MRI examination; Nisreen A.A. Mohammed guide the work throughout the study; Walaa H. Mohamed carried out full clinical assessment of the patients; and Ahmed M. Hamed conceived the study and its design; all authors have read and approved the final manuscript.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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