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# Role of Diffusion Weighted Imaging and Apparent Diffusion Coefficient Value in Diagnosis of Asymptomatic / Inactive Multiple Sclerosis Plaques

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**ABSTRACT**

**Background:** Although in most cases, the diagnosis of MS remains a clinical, magnetic resonance imaging became a fundamental imaging technique for the investigation and monitoring patients with MS, as it allows the visualization of lesions in the brain and spinal cord and help in understanding and follow of the disease and it is widely used to confirm the clinical diagnosis.
**Aim of The Work:** To evaluation of asymptomatic or inactive multiple sclerosis plaques by using diffusion weighted imaging and ADC value.
**Patients and Methods:** We evaluated prospectively 50 patients with known multiple sclerosis and fulfilled McDonald Criteria 2017. Patients of interest were recruited from the Neurology department in Al-Azhar University Hospitals during two years (May 2020 to May 2022). Clinical diagnosis was performed by an expert neurologist with 10 years of experience in treating MS.
**Results:** Receiver operator characteristics (ROC) curves for ADC value x (10−3 mm2/s) as a predictor of activity of the M.S disease in enrolled patients. ADC value x (10−3 mm2/s) indices were significant predictors as denoted by the significantly large area under the curves (AUCs), there was used to define the best cut off value of ADC value x (10−3 mm2/s) which was ≥1.292, with sensitivity of 82.1% specificity of 82.6% positive predictive value of 85.2%, negative predictive value of 79.2%, diagnostic area under the curve of 0.828 with p-value <0.001.
**Conclusion:** Measurement of ADC value should be done as a routine study with conventional MRI in MS patients.

**Keywords:** *Inactive Multiple Sclerosis Plaques; DWI; ADC.*

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## INTRODUCTION

Multiple sclerosis (MS) is the most common demyelinating and neurodegenerative inflammatory disease in adults between 18 and 35 years of age and constitutes the second cause of neurological disability in young adults.[1]

This pathology is considered an autoimmune organ specific disorder, characterized by multiple focal areas of demyelination called plaques or lesions, which are accompanied by different degrees of gliosis, inflammation, and neuroaxonal damage.[2]

In the examination and diagnosis of MS, MRI is a crucial tool. Multiple, hyper-intense plaques characterize MS plaques in T2 Weighted Images (WI) and Fluid Attenuated Inversion Recovery (FA IR) (FL AIR). T1WI lesions with low intensity ("black holes") are linked to myelin atrophy. Contrast-enhancing lesions indicate a breakdown of the blood-brain barrier due to acute inflammation; if managed with steroids, enhancement can last for 2 to 6 weeks. 3 & 4

In early and asymptomatic MS plaques, MRI has a high sensitivity. The sensitivity of MRI for spinal cord injuries ranges amongst articles, ranging from 68 to 89 percent. [1]

MS plaques generally occur in the white matter although 10% of the plaques are seen in the gray matter. The MS plaques are generally seen in the capsula interna, periventricular white matter, corpus callosum and pons.[5]

The Apparent Diffusion Coefficient (A D C) of water in the brain can be measured using a Diffusion Weighted Image (D W I). Water diffusion in the brain is regulated by cellular borders, and any breakdown in cellular structure raises the A D C. [6]

The random translational motion of molecules caused by their internal thermal energy is known as diffusion. It is now possible to derive information on the structural organization of tissues well beyond the spatial resolution of standard M R imaging techniques thanks to the advancement of M R quantifiable diffusion effects. Spin echo-based sequences are used in DWI, and high

magnetic field gradient pulses are used to sensitize diffusion. [7]

The goal of the study was to use diffusion weighted imaging and the ADC value to assess asymptomatic or inactive multiple sclerosis plaques.

## PATIENTS AND METHODS

We evaluated prospectively 50 patients with known multiple sclerosis and fulfilled McDonald Criteria 2017. Patients of interest were recruited from the Neurology department in Al-Azhar University Hospitals during two years (May 2020 to May 2022). Clinical diagnosis was performed by an expert neurologist with 10 years of experience in treating MS.

Inclusion criteria: Both female and male with age group (20 – 45) years old who were referred with multiple sclerosis remission state (asymptomatic patients) for follow up and other symptomatic patients with multiple sclerosis were enrolled in the study.

Exclusion criteria: Patients known to have contraindications for MRI, e.g. an implanted magnetic device, pacemakers, patients who have claustrophobia, patients with past history of intracranial surgical interference, patients with bad general condition needing life support, and patients with other forms of MS and patients for whom there were no MRI images were excluded from the study.

Ethical considerations: Oral and written consents were obtained from all patients prior to inclusion them in the study. The study was conducted according to the stipulations of Al-Azhar university ethical and scientific committee.

Patient preparation:

Full history taking from each patient including name, gender, age, complain, duration of the disease, treatment. And clinical examination done by the neurologist.

Detailed explanation of imaging procedure. Removal of cards and any other metal containing objects. Contrast injection benefits and risks was explained to the patient before the scan. Fasting for 6 – 8 hours and checking serum creatinine before Gadolinium administration. Measuring patient body weight for calculation of amount of contrast media, and instruct the patient to keep calm.

Conventional MRI was done using a phased array head coil, with 1.5 Tesla MRI scanner (Philips achieva XR). In Al-Azhar University Imaging Unit.

Statistical analysis:

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Independent-samples t-test of significance was used when comparing between two means. Chi-square ($x^2$) test of significance was used in order to compare proportions between qualitative parameters. Receiver operating characteristic (ROC curve) analysis was used to find out the overall predictivity of parameter in and to find out the best cut-off value with detection of sensitivity and specificity at this cut-off value. The confidence interval was set to 95% and the margin of error accepted was set to 5%. P value < 0.05 was considered significant.

## RESULTS

| Plaques distribution about Number of patients | Symptomatic group (n=25) | Asymptomatic group (n=25) | $x^2$ | p-value |
|---|---|---|---|---|
| **Subcortical** | 14 (56.0%) | 10 (40.0%) | 1.256 | 0.262 |
| **Jucustacortical** | 23 (92.0%) | 21 (84.0%) | 0.742 | 0.389 |
| **Periventricular** | 23 (92.0%) | 24 (96.0%) | 0.348 | 0.556 |
| **Spinal cord** | 6 (24.0%) | 1 (4.0%) | 4.070 | 0.044* |
| **Brain stem** | 5 (20.0%) | 5 (20.0%) | 0.000 | 1.000 |
| **Cerebellar peduncle** | 4 (16.0%) | 0 (0.0%) | 4.261 | 0.039* |

Using: x2: Chi-square test; p-value>0.05 NS; *p-value <0.05 S; **p-value <0.001 HS

**Table 1:** Comparison between symptomatic group and asymptomatic group according to plaques distribution about number of patients.

There was a significant difference in the sites of M.S plaques in spinal cord and cerebellar peduncles between symptomatic and asymptomatic groups P< 0.05. While no significant difference in the subcortical, juxtacortical, periventricular and brain stem P>0.05 (Table 1).

| Number of plaques | Symptomatic group (No. of Plaques= 367) | Asymptomatic group (No. of Plaques= 327) | $x^2$ | p-value |
|---|---|---|---|---|
| **Subcortical** | 55 (15.0%) | 25 (7.6%) | 9.281 | 0.002* |
| **Juxtacortical** | 107 (29.2%) | 93 (28.4%) | 0.054 | 0.817 |
| **Periventricular** | 179 (48.8%) | 198 (60.6%) | 9.691 | 0.002* |
| **Spinal cord** | 12 (3.3%) | 3 (0.9%) | 4.687 | 0.030* |
| **Brain stem** | 6 (1.6%) | 8 (2.4%) | 0.570 | 0.450 |
| **Cerebellar peduncle** | 8 (2.2%) | 0 (0.0%) | 7.268 | 0.007* |

Using: x2: Chi-square test; p-value>0.05 NS; *p-value <0.05 S; **p-value <0.001 HS

**Table 2:** Comparison among number of M.S plaques in differents sites between symptomatic group and asymptomatic groups.

There was a statistically significant difference between number of MS plaques in between symptomatic and asymptomatic patients in subcortical, spinal cord and cerebellar peduncles in all these sites the number of plaques were more in symptomatic patients P<0.05 .While the periventricular site plaques were more in asymptomatic patient P<0.05. Other plaques sites including juxtacortical and brain stem show no significant difference P>0.05 (Table 2).

| MRI | Symptomatic group (No. of Plaque= 367) | Asymptomatic group (No. of Plaque= 327) | Test value | p-value |
|---|---|---|---|---|
| **Plaque diameter (mm)** | | | | |
| **Mean±SD** | 11.39±2.35 | 10.06±1.61 | t=8.594 | 0.008* |
| **Range** | 6-16 | 7-13 | | |
| **TW2** | | | | |
| **Hyper intense** | 367 (100%) | 327 (100%) | $x^2$=0.000 | 1.000 |
| **FLAIR** | | | | |
| **Hyper** | 367 (100%) | 327 (100%) | $x^2$=0.000 | 1.000 |
| **TW1** | | | | |
| **Hypo intense** | 5 (1.4%)6 | 3 (0.9%) | $x^2$=0.037 | 0.848 |
| **Iso intense** | 362 (98. %) | 324 (99.1%) | | |
| **DWI-b 1000** | | | | |
| **Hyper** | 27 (7.3%) | 15 (4.5%) | $x^2$=1.586 | 0.208 |
| **Iso intense** | 337 (91.8%) | 307 (93.8%) | | |
| **Hypo intense** | 3 (0.8%) | 5 (1.5%) | | |
| **DWI- b0** | | | | |
| **Hyper** | 367 (100%) | 327 (100%) | $x^2$=0.000 | 1.000 |

Using: t=Independent Sample t-test; x2: Chi-square test; p-value>0.05 NS; *p-value <0.05 S; **p-value <0.001 HS

**Table 3:** Comparison among M.S plaques regarding MRI finding between symptomatic and asymptomatic groups.

There was a statistically significant difference between diameters of M.S plaques between symptomatic and asymptomatic groups, p-value (p<0.05). The diameter was more in symptomatic group. There was no statistically significant difference in the MRI sequences finding of M.S plaques between symptomatic and asymptomatic patients, P >0.05) (Table 3).

| ADC | Symptomatic group (No. of Plaque= 367) | Asymptomatic group (No. of Plaque= 327) | $x^2$ | p-value |
|---|---|---|---|---|
| **Hyper** | 349 (95.1%) | 319 (97.6%) | 2.256 | 0.133 |
| **Hypo** | 18 (4.9%) | 8 (2.4%) | | |

Using: x2: Chi-square test; p-value >0.05 NS

**Table 4:** Comparison M.S plaques MRI ADC finding between symptomatic group and asymptomatic group.

There was no significant difference in the number of restricted M.S plaques between symptomatic and asymptomatic patients P >0.05), restricted plaques (hyper intense in DWIb1000 and hypo intense in ADC) were more in symptomatic patients then in asymptomatic patient with not reaching statistical difference (Table 4).

| ADC value x ($10^{-3}$ mm2/s) | Symptomatic group (No. of Plaques= 349) | Asymptomatic group (No. of Plaques= 319) | t-test | p-value |
|---|---|---|---|---|
| **Mean±SD** | 1.43±0.21 | 1.18±0.19 | 16.370 | <0.001** |
| **Range** | 1.029-1.869 | 0.979-1.623 | | |

Using: t=Independent Sample t-test; **p-value <0.001 HS

**Table 5:** Comparison between symptomatic group and asymptomatic group regarding ADC value x (10−3 mm2/s) in the Shine Through plaques.

The mean value of ADC was higher in symptomatic patients than in asymptomatic patients 1.43±0.21 and 1.18±0.19 x (10−3 mm2/s) respectively with high significant difference P<0.001 (Table 5).

| ADC value x ($10^{-3}$ mm2/s) | Symptomatic group (No. of Plaque= 18) | Asymptomatic group (No. of Plaque=8) | t-test | p-value |
|---|---|---|---|---|
| **Mean±SD** | 0.79±0.08 | 0.72±0.25 | 1.333 | 0.259 |
| **Range** | 0.67-0.93 | 0.15-0.87 | | |

**Table 6:** Comparison between ADC value of restricted M.S plaques between symptomatic group and asymptomatic group.

There was no important variance in the A DC value of the restricted M.S plaques in both symptomatic and asymptomatic patient P>0.05 (Table 6).

| | Symptomatic group (No. of Plaque= 367) | Asymptomatic group (No. of Plaque= 327) | $x^2$ | p-value |
|---|---|---|---|---|
| **Enhancement** | | | | |
| **No** | 352 (95.9%) | 319 (97.6%) | 0.986 | 0.321 |
| **Enhanced** | 15 (4.1%) | 8 (2.4%) | | |
| **DWI** | | | | |
| **Restricted** | 18 (4.9%) | 8 (2.4%) | 2.256 | 0.133 |
| **Shine Through** | 349 (95.1%) | 319 (97.6%) | | |

**Table 7:** Comparison between symptomatic group and asymptomatic group regarding enhancement of M.S plaques in post contrast T1 MRI sequence and DWI appearance.

T1post contrast enhancement of M.S plaques was more detected in the symptomatic patients than in asymptomatic patient as well as the restricted plaques were more in symptomatic than in asymptomatic patients but with no important variance in P >0. 05 (Table 7).

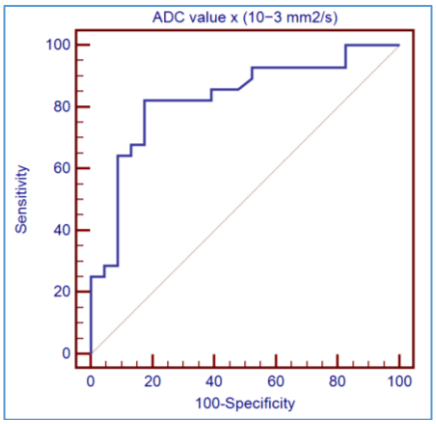
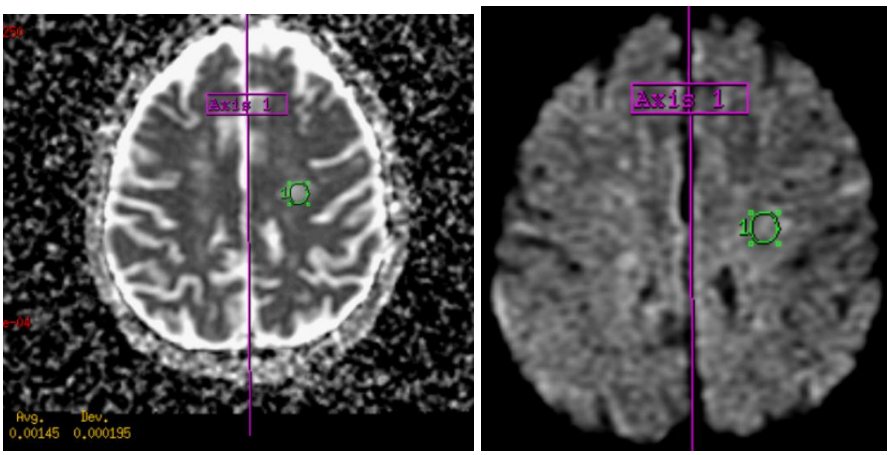


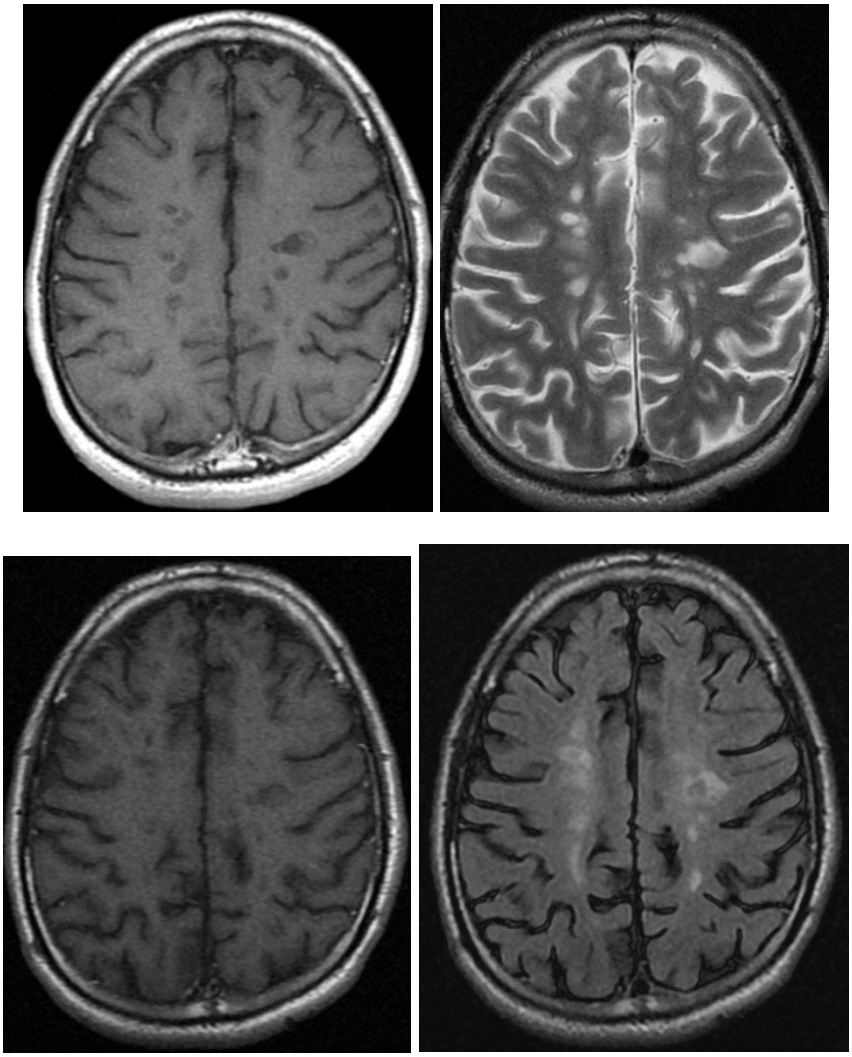

**Fig. 1:** Receiver-operating characteristic (ROC) curve for a prediction of activity of the disease using ADC value x (10−3 mm2/s).

| Cut-off | Sen. | Spe. | PPV | NPV | AUC [95% C.I.] | p-value |
|---|---|---|---|---|---|---|
| **≥1.292** | 82.1% | 82.6% | 85.2% | 79.2% | 0.828 [0.697-0.919] | <0.001 |

Receiver operator characteristics (R OC) curves for ADC value x (10−3 mm2/s) as a predictor of activity of the M.S disease in enrolled patients. ADC value x (10−3 mm2/s) indices were significant predictors as denoted by the significantly large area under the curves (AUCs), there was used to define the best cut off value of ADC value x (10−3 mm2/s) which was ≥1.292, with sensitivity of 82.1% specificity of 82.6% positive predictive value of 85.2%, negative predictive value of 79.2%, diagnostic area under the curve of 0.828 with p-value <0.001 (Figure 1).

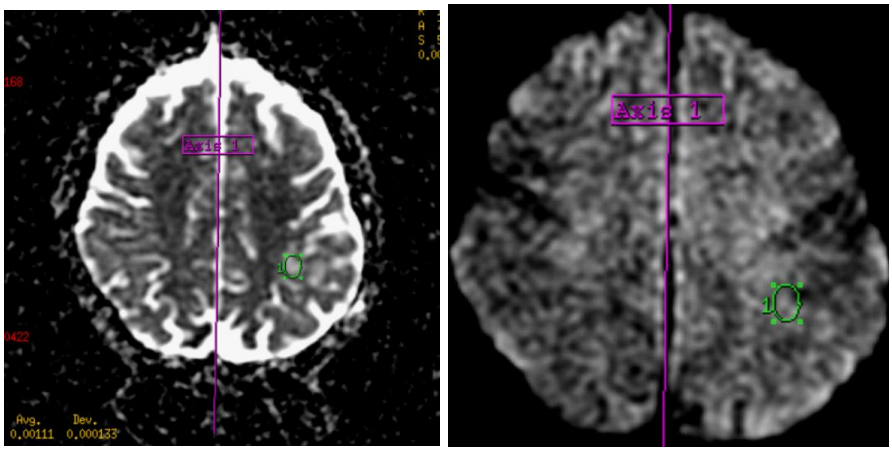
CASES

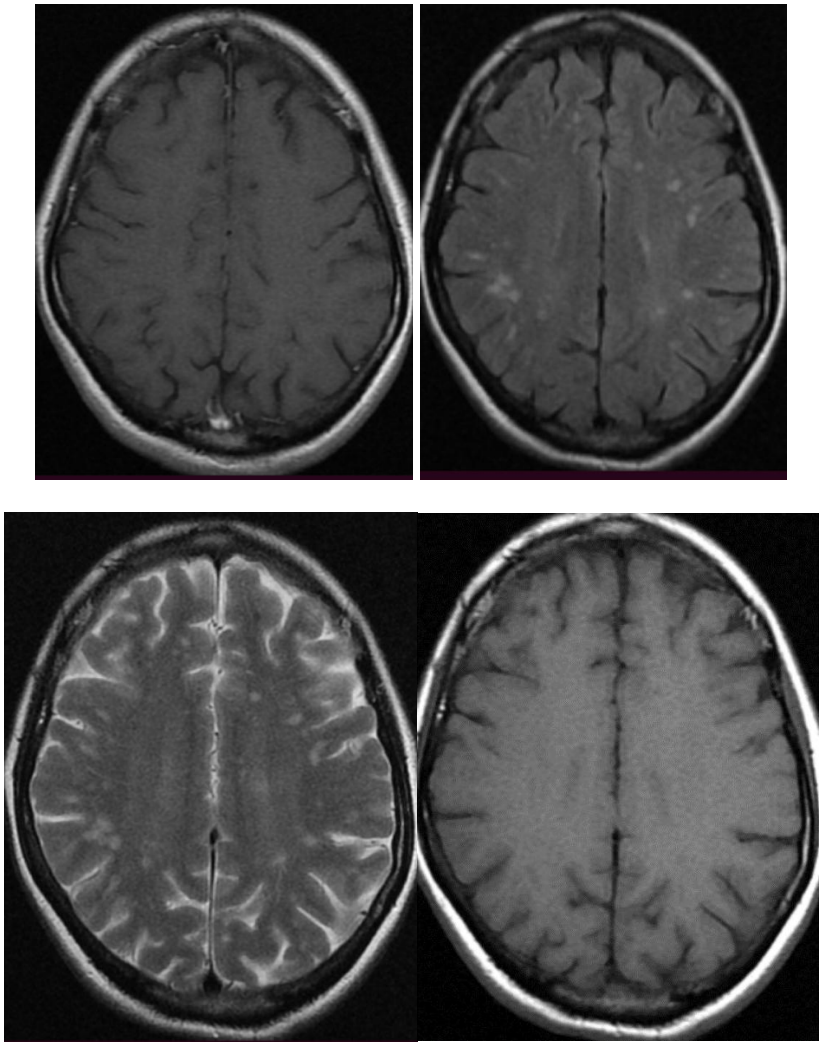




Case (1): 38 years old male with 4 years history of multiple sclerosis, presented with limb weakness at time examination;

Figure (2): MRI shows presence of about 40 MS plaques, supratentonrial, biggest plaque was 9 mm, appears hyperintense in T2W, hyperintense in FLAIR, hypointense in T1W, not enhanced post contrast, shine through in ADC, it's value was 1.45 x 10-3mm2/s





Case (2): 33 years old male had history of MS for 2 years, in remission state presented for follow up,

Figure (3): MRI findings were presence of 22 MS plaques, supratentorial, biggest one 12 mm, appears hyperintense in T2W and FLAIR, isointense inT1W, hyperintense in ADC, its value was 1.11 x 10-3 mm2/s.

## DISCUSSION

In Egypt, no strong evidence about the validity of ADC in diagnosis, monitoring or differentiation of lesions or compare its value in symptomatic and asymptomatic patients with MS, therefore, the current study aimed to assess the validity of ADC values among Egyptian patients with MS and compare the values in aysmptomatic and symptomatic patients. Hence, a total of 50 Egyptian MS patients were enrolled in this study.

In the current study and as a part of study design, the 50 patients assigned into two groups with 25 patients in each, symptomatic and asymptomatic group. Regarding the reported symptoms among symptomatic group, limb weakness was the more frequent (36%) followed by parasthesia in 24% then cognitive disturbance and vision disturbance in 20% for each. The clinical features of MS are not similar in MS patients also it vary from one population to another as the MS is complicated neuro-degenerative disease associated with different clinical features depending on the extent and site of the lesions.[8, 9]

The current study found that in majority of patients the plaques were supratantorial, periventricular, Jucostacortical and subcortical, other sites were less frequent, these findings agreed that reported by Arevalo et al.[10], who documented that typical plaque locations are the subcortical WM (U fibers), periventricular WM, and posterior fossa.

The difference in age was statistically significant where symptomatic patients were younger than asymptomatic, the mean age was 28.32 and 32.64 years, respectively, ($P<0.05$), this difference could be explained firstly, older age at onset associated with asymptomatic form of the disease, on the other hand asymptomatic patients had symptoms affected by relapse-remission status, similarly, Granella et al.[11] found that older age was significantly associated with asymptomatic disease. Moreover, it is widely postulated that clinical and sub-clinical activity of MS decreases with aging.[13]

Moreover, in this study the duration of disease was significantly longer in asymptomatic than symptomatic group, the mean duration was 5.12±2.71 vs. 1.25±1.19, respectively, ($P<0.001$).

Kappos et al.[13] and Cerqueira et al.[14] reported significant decrease in disability symptoms and progression when the disease duration increased particularly in those diagnosed within 10 years. This may be due to the earlier treatment of the disease, where it had been confirmed that even in late stage of MS duration of disease is a key factor in the effect of treatment,[15] despite the fact that the effect of medications may reduce with duration and natural history of the disease.[16]

The present study found that vast majority (96.3%) of plaques were hyper intense in ADC and the mean ADC value was 1.32±0.24 for the total patients. Out of the total 694 plaques, only 23 (3.3%) were enhanced the remaining plaques were not, and more than two thirds, 69.6%, of these plaques of mural enhancement and the remaining 30.4% of ring pattern of enhancement. On the other hand 26 plaques (3.7%) were restricted (hyper intense in DWIb1000 and hypo intense in ADC). The enhancement and its pattern reported in our study could be attributed to the new lesions and early activity of the diseases that may show transient contrast enhancement which could be due to gadolinium leakage that typically last for 2-6 weeks.[17, 18]

In the current study, comparison between symptomatic and asymptomatic groups according to site of plaques revealed no significant difference in all sites except spinal cord lesions and cerebellar peduncle where the plaques were more frequent in these site in symptomatic than asymptomatic group, ($P<0.05$). Bot et al.[18] confirmed that spinal cord abnormalities were more frequent in recently diagnosed symptomatic patients. However, some case series documented that some asymptomatic MS patients may diagnosed by chance during the MRI examination indicated for other diseases other than suspected inflammatory demyelinating disease of CNS, in these cases the situation referred as radiologically isolated syndrome as a common type of MS.[19]

The present study comparison of MRI ADC of M.S plaques in symptomatic and asymptomatic group revealed that mean ADC value in symptomatic group was significantly higher than that in asymptomatic group; 1.43±0.21 vs. 1.18±0.19 x ($10^{-3}$ $mm^2/s$), respectively, ($P<0.001$). This finding indicated an association between disease activity and ADC values and consistent with that reported in previous studies[20, 21,22]

Additionally, ADC value were not significantly different between restricted plaques on DWI in symptomatic and asymptomatic MS patients (37). Also no significant differences were found in the number of plaques that enhanced or not despite that, T1post contrast enhancement of M.S plaques was more detected in the symptomatic than asymptomatic patient as well as the restricted plaques were more in symptomatic than in asymptomatic patients but not reach significant level.

To assess the validity of ADC value in symptomatic and asymptomatic patients, ROC curve analysis was performed and showed that ADC value was significant predictor of symptomatic MS at cutoff point of 1.292 it has a sensitivity of 82.1% and specificity of 82.6% with an accuracy of 82.4%, the positive predictive value of 85.2%, negative predictive value of 79.2%, and a diagnostic area under the curve of 0.828 reflected that ADC was good and valid predictor of disease activity, these findings agreed that reported in previous studies; Mohammed and Ismail[21] concluded that ADC value was more valuable predictor in assessment of activity of MS, on the other hand, they found that ADC value can predict the histological changes in MS lesions but did not associated with the pattern of enhancement.

Another study conducted by Almolla et al.[23], documented that ADC was significantly correlated to cognitive impairment in MS patients with relapse remittent form with regard to the plaque number, periplaque and normal white matter. A recent Egyptian study conducted by Ragheb et al.[22] found that ADC value of normal white matter and MS can be used to differentiate MS and assessment of clinical subtypes and also can be helpful in follow up of progression of disease as it showed strong correlation with the degree of progression. Furthermore, Ragheb et al. [22] also assessed the value of ADC in differentiation between relapsing remittent from progressive cases and found that at cutoff point of 1.3 $x10^{-3}$ $mm^2/sec$ ADC had a sensitivity of 89.3%, specificity of 85% and accuracy of 80%, which are close to our results.

Paavilainen et al.[24] assessed the validity of ADC in the follow up of cases with relapsing remittent MS cases and reported that changes in activity of disease could be associated with both lower and higher values of ADC and the change in ADC values attributed to inflammatory changes in normally appearing brain tissue during inflammatory activity and related mainly to the resolution during less active inflammatory process.

Unal et al.[25] study aimed to evaluated the value of ADC in active and non-active lesions; authors demonstrated no significant difference in ADC values between active and non-active lesions. Nonetheless, they attributed the increase in ADC values to the damage of tissue and extracellular space enlargement. These data indicated that microscopic injuries are not significant in early stages of MS.

## CONCLUSION

Measurement of ADC value should be done as a routine study with conventional MRI in MS patients. DWIb0 can replace T2W sequence in ill patient as the DWIb0 need shorter time than T2W, since all MS plaques are visualized in DW1b0 as hyper intense focus as in T2W. Niether plaque restrictor nor enhancement can differentiate symptomatic MS patients from asymptomatic patient**.**

ADC mean values is a good predictor to differentiate symptomatic from asymptomatic MS patients with significant difference $P< 0.001$. A large area under the curves (AUCs =0.828), with best cut off value of ADC value x (10−3 mm2/s) which was ≥1.292, with sensitivity of 82.1% specificity of 82.6% positive

predictive value of 85.2%, negative predictive value of 79.2%.

Conflict of interest : none

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