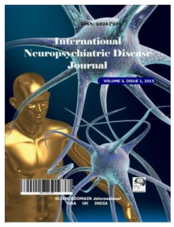

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Diffusion-weighted MR Imaging of the Brain: Correlation of Ischemic Lesion Patterns with ASCO Stroke Subtypes

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Authors' contributions

This work was carried out in collaboration between all authors. Author AAZ designed the study and wrote the protocol and the final draft of the manuscript. Authors AAE and MES managed the literature searches. Authors AAKAR and AAZ wrote the first draft of the manuscript. Author AAKAR managed the radiology results. Authors MES and AAZ performed the clinical data collection. Authors AAE and MES performed the statistical analysis. All authors read and approved the final manuscript.

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ABSTRACT

Background: There are many etiologies for ischemic cerebral stroke. Previous studies have not shown whether specific ischemic lesion patterns on early brain diffusion-weighted imaging (DWI) are associated with specific ischemic stroke causes.
Objective: This study was designed to correlate the pattern and distribution of ischemic lesions on (DWI) with ASCO stroke subtypes [atherosclerosis (A), small vessel disease (S), cardiac source (C), and other cause (O)].
Subjects and Methods: We retrospectively evaluated patients with ischemic lesions within 72 hours of stroke onset who underwent brain DWI. Ischemic lesions were classified as single, scattered and multiple. The stroke subtypes were classified according to ASCO criteria.

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Results: A total of 490 patients was studied, (285 Males, 205 females) with a mean age of 69.8± 10.4 years. We found (A) (N=180), (S) (N=70), (C) (N=145) and (O) (N=95). In patients with (A) the scattered anterior circulation lesions were statistically significant (45 patients, P=0.04). With (S) the most common and only pattern was to single subcortical lesion (70 patients, P=0.000). While, with (C), the statistical significance was to single cortical, multiple unilateral anterior circulation, single subcortical, and scattered anterior circulation respectively (65, 45, 15 and 15 patients, P=0.01, 0.02, 0.03, and 0.03). Patients with (O) were highly statistically significantly associated with single subcortical lesions (40 patients, P=0.000).
Conclusion: There is a significant correlation between the ASCO stroke subtypes and DWI patterns which assisted in determining the stroke etiology.

Keywords: Diffusion weighted MRI; ASCO stroke subtypes; ischemic stroke; atherosclerosis.

1. INTRODUCTION

Stroke, especially ischemic type, is caused by many etiologies that require different preventive measures. Analyzing the causes of stroke subgroups may help to explain regional differences in stroke incidence and also to reduce the burden of stroke in the future [1]. One of the newest ischemic stroke classifications is ASCO (A for atherosclerosis, S for small vessel disease, C for the cardiac source, O for other cause). In phenotypic system (ASCO), every stroke patient's etiological pathology can be characterized, as well as acknowledgment made of the strength of the diagnostic evidence. Each of the four phenotypes (A, S, C, and O) is graded 1, 2 or 3, based on a level of diagnostic certainty. Also, the phenotype is given a grade of 0 if there is no evidence after a thorough investigation, or a grade 9 if there was insufficient work-up to make a determination [2].

Diffusion-weighted (DW) MR imaging already has a substantial impact on early stroke management. On the contrary, to CT and conventional MR imaging, DW imaging provides the uncovering of lesions in the first hours after the onset of clinical symptoms. Furthermore, DW imaging is superior in detecting very tiny ischemic lesions due to the high signal intensity-to-noise ratio and has the capacity of differentiating between chronic and acute lesions [3]. Clinically silent, small lesions may influence the diagnosis of stroke subtype in ischemic stroke when multiple lesions are detected on DW imaging [4]. The presence of multiple ischemic lesions suggests embolism from the heart or the aortic arch or stenosis of one of the intracranial large arteries if confined to one vascular territory. While, multiple infarcts in more than one vascular territory, especially in bilateral lesions, agreed strongly for a proximal source or systemic cause [5]. Patients with ischemic lesions due to multiple emboli may be at a higher risk of stroke recurrence in the acute phase and therefore may benefit from a specific therapy, for example, anticoagulation. So, diffusion-weighted imaging is superior to other diagnostic modalities in the early detection of hyperacute stroke, multiple embolic strokes, and small ischemic lesions [6]. When performed within 24 hours of hospital admission, magnetic resonance angiography and DWI improve the accuracy of early diagnosis of stroke subtype [7].

There have been several studies addressing the correlation between ischemic lesion topography on DWI and stroke subtypes. Those studies, however, yet, were limited to the specific stroke cause or pattern [8] or considered only multiple ischemic lesions [9,10,11,12]. None of the previous studies have addressed the question whether specific ischemic lesion patterns on early DWI are associated with particular ischemic stroke causes. Thus, lesion patterns may be closely associated with stroke etiology and may have significant clinical consequences. Therefore, we investigated the association of the stroke subtype defined by ASCO criteria in stroke patients by using Diffusion-weighted MR imaging.

2. PATIENTS AND METHODS

2.1 Patients

Approval of this study was obtained from the ethical committee of Mansoura University Hospital. Informed consent was waived because this is a retrospective study. Retrospective analysis of a natural history study of cerebrovascular disease in all patients was done. Patients with neurologic symptoms due to an etiology other than cerebral ischemia were excluded. We studied patients with a final diagnosis of ischemic stroke who had an acute lesion corresponding to a clinical syndrome on

DWI performed within 72 hours of stroke onset. While the final diagnosis of ischemic stroke was made when patients presented with signs or symptoms of new-onset stroke lasting for 24 hours or longer. The time from the onset of stroke was determined at the time the patients were last known to be without their new ischemic symptoms.

2.2 Routine Assessment for Ischemic Stroke

They include the following blood tests, urinalysis, chest radiographs, electrocardiographic monitoring, transthoracic echocardiography, and carotid ultrasonography.

2.3 Stroke Subtype Classification

We classify patients, according to the new approach to stroke subtyping, (ASCO classification of stroke). Every patient is characterized by A-S-C-O: A as for atherosclerosis, S as for small vessel disease, C as for the cardiac source, O as for other cause.

2.4 DWI Assessments

Imaging was performed using a 1.5 T MR machine (Symphony; Siemens AG Medical Systems, Forchheim, Germany). Diffusion-weighted imaging had the following variables: b-values of 0 mm^2 s^{-1}, 500 mm^2 s^{-1} and 1000 mm^2 s^{-1} while TR/TE of 1000/108 ms, band width=125 KHz and slice thickness = 4mm. Ischemic lesions on DWI were classified into single lesions (cortical, subcortical, cortico-subcortical), scattered lesions in one vascular territory, or multiple lesions in more than one vascular territory. Multiple DWI lesions were defined as multiple noncontiguous hyperintense lesions in more than one vascular territory. The vascular territories were divided for the anterior circulation as the anterior cerebral artery, the middle cerebral artery (lenticulostriate, inferior division, and superior division), a single penetrating artery in the deep structure (white matter), watershed and the anterior choroidal artery; and for the posterior circulation as the posterior cerebral artery, cerebellar arteries, the circumferential branches of the basilar artery (superior, anterior inferior and posterior inferior) and cerebellar watershed. The topography of ischemic lesions of the vascular territory was determined by reference to published templates.

2.5 Statistical Analysis

One DWI lesion pattern and one stroke subtype were determined in each patient. We evaluated the overall association of the 10 DWI lesion patterns with seven stroke subtypes by Pearson X^2 test with Monte Carlo approximation. We also assessed the relationship of each DWI lesion pattern with stroke subtype in a pairwise fashion using the Fisher exact test. A2-tailed $P<.05$ was considered statistically significant.

3. RESULTS

A total of 490 patients with ischemic stroke was studied, (285 Males, 205 females) with a mean age of 69.8± 10.4 years. The most common prevalent vascular risk factors were dyslipidemia (41.5%), current smoking (25%), family history of stroke (22%), coronary heart disease (20%), atrial fibrillation (15%), peripheral arterial disease (10%), and myocardial infarction (3.5%) while, the mean body mass index (BMI) was 24.8±1.5. Regarding the use of secondary preventive drugs, antithrombotic, antihypertensive drugs, statins, oral hypoglycemic drugs, and insulin usage 74.3%, 63.5%, 55.6%, 15.4%, and 4.7% respectively. Moreover, the mean value of NIHSS score was 15.3 ± 12.5 while, the percentage of MS Rankin score equal, or less than two was 40.8%, and the more than two was 59.2% (Table 1).

The distribution of the etiology of ischemic stroke with ASCO subtypes according to their frequency was as follows: 36.7% (180/490) had the large artery disease (A), 29.6% (145/490) a cardiac source (C), 19.4% (95/490) another cause (O) and 14.3% (70/490) small vessel disease (S) (Table 2) (Figs. 1, 2 and 3).

In patients with (A) the scattered AC lesions, MRD pattern showed the statistically significant differences (45 patients, P=0.04). In patients with (S), the most common and only MRD pattern was to single subcortical lesion (70 patients, P=0.000) with high statistical significance. Patients with (C), the statistical significant were single cortical, multiple unilateral anterior circulation, single subcortical, and scattered anterior circulation respectively (65, 45, 15 and 15 patients, P=0.01, 0.02, 0.03, and 0.03). Patients with (O) were highly statistically significantly associated with single subcortical lesions (40 patients, P=0.000). The majority of stroke patients with cortical and subcortical infarcts are due to either atherosclerosis (30.5%)

or cardiac causes (41.3%) without statistical significance. On the other hand, the majority of stroke patients with single subcortical are due to small vessel disease (100%) (Table 3).

Table 1. General characteristics of the studied patients

Variable		Patients (N= 490)
Demographic data		
Age (years)		69.8± 10.4
M/F (M:F)		285/205 (1.3:1)
Vascular risk factors		
Family history of stroke		22%
Diabetes (%)		18%
Hypertension (%)		72%
Atrial fibrillation (%)		15%
Coronary heart disease		20%
Myocardial infarction		3.5%
Peripheral arterial disease		10%
Current smoking		25%
Dyslipidemia		41.5%
Mean BMI		24.8±1.5
Secondary preventive drugs		
Antithrombotics		74.3%
Antihypertensive drugs		63.5%
Statins		55.6%
Oral hypoglycaemic drugs		15.4%
Insulin		4.7%
Clinical scales		
NIHSS		15.3 ± 12.5
MS Rankin score	≤2	40.8%
	>2	59.2%

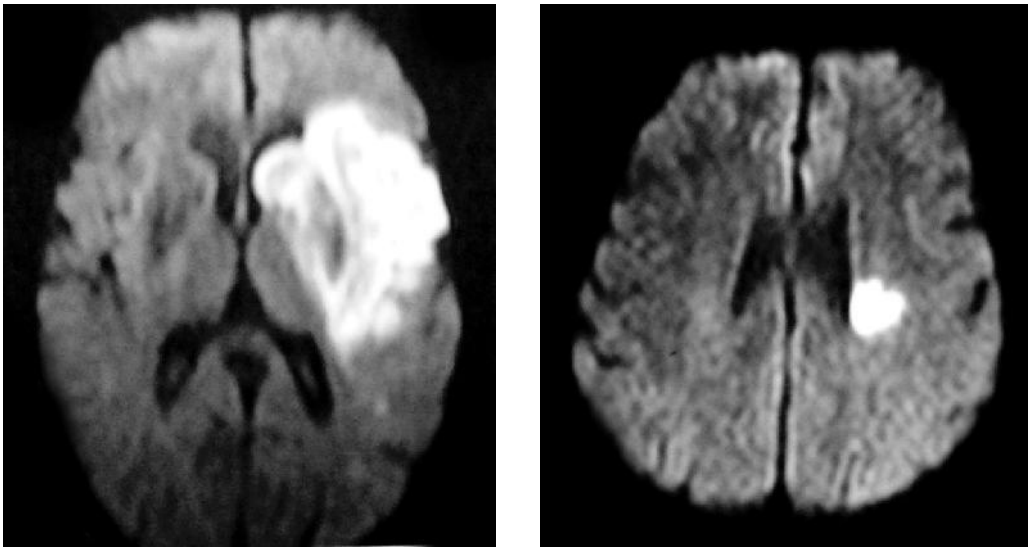
4. DISCUSSION

Physicians usually intuitively determine the subtypes of ischemic stroke based on clinical features and the results of diagnostic studies. While this nonstandardized approach may be acceptable for clinical practice, a clinical trial should strive for uniform diagnoses to obtain greater interphysician consistency. The diagnostic features must be widely fair, easy to use and sufficiently pragmatic that physicians in other situations can also use them [13].

ASCO is a typical phenotype system that categorizes stroke patients, depending on their etiologic characteristics [14]. The definitions for subtypes are mainly based on expert opinion and are slightly different from those in other systems. The confirmed diagnosis of atherothrombosis is considered when there are atherosclerotic plaques in the clinically relevant artery causing more than 70% stenosis or less than 70% stenosis with attached thrombus in the lumen, or mobile thrombus in the wall of the aortic arch. The assured diagnosis of small vessel disease requires the demonstration of a deep infarct with a diameter less than 15 mm plus the presence of old lacunar infarct or leukoaraiosis or repeated, recent, similar transient ischemic attacks. In the meanwhile, cardiac sources of embolism are graded arbitrarily into various risk groups based on their relative potential to cause a stroke. This classification system incorporates the quality of diagnostic evaluation in its subtype assignments in different grades: 0 for conditions in which diagnostic evaluation reveals no abnormal

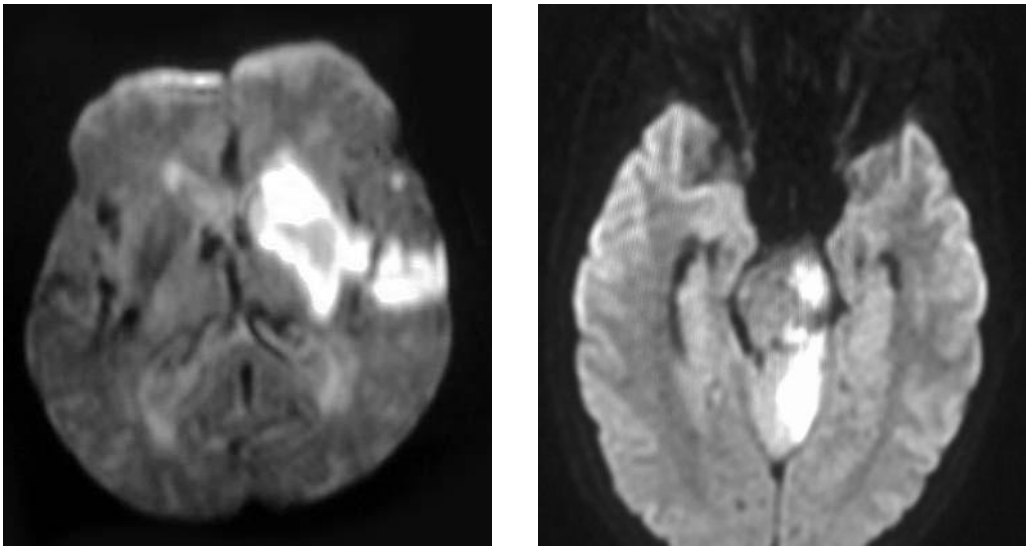
Table 2. The distribution of MRD lesion patterns of ischemic cerebral stroke patients (n=490) with ASCO classification

MRD lesion patterns		A N (%)	S N (%)	C N (%)	O N (%)	Total N (%)	
Single	Cortical	60 (33.3)	-	65 (44.8)	15 (16)	140 (28.6)	290
	Subcortical	25 (14)	70 (100)	15 (10.4%)	40 (42)	150 (30.6)	(59.2)
Scattered	AC	45 (24.8)	-	15 (10.4)	25 (26)	85 (17.3)	100
	PC	10 (5.6)	-	5 (3.5)	-	15 (3.1)	(20.4)
Multiple	AC unilateral	30 (16.7)	-	-	15 (16)	45 (9.2)	100
	Bilateral AC & PC	10 (5.6)	-	45 (31.1)	-	55 (11.2)	(20.4)
Total		180 (36.7)	70 (14.3)	145 (29.6)	95 (19.4)	490 (100)	



(A) (B)

Fig. 1. Single lesion: (A) Diffusion weighted MR image shows large cortical-subcortical lesion along the territory of middle cerebral artery. (B) Diffusion weighted MR image shows subcortical infarction



(A) (B)

Fig. 2. Scattered lesions: (A) Diffusion weighted MR image shows scattered lesions along the territory of the right middle cerebral artery. (B) Diffusion weighted MR image shows lesions in the left side of brainstem

feature, 1 for the presence of a definite cause based on direct demonstration by a gold standard test, 2 for the existence of an obscure cause based on evidence from tests with imperfect sensitivity and specificity, 3 for situations in which disease is present but not likely a direct cause of stroke, and 9 for the incapability to perform relevant diagnostic tests for a given subtype. ASCO explains clinically and pathogenically important groups. Although it is realistic, it is not illustrative, and based on the minimum number of necessary investigations and an appropriate work-up to make classification possible [14].

Table 3. Comparison between different ASCO subtypes

MRD Lesion patterns		A Vs non A		S Vs non S		C Vs non C		O Vs non O	
		Test of sig.	P value	Test of sig.	P value	Test of sig.	P value	Test of sig.	P value
Single	Cortical	0.64	0.5	2.03	0.04*	2.08	0.01*	1.81	0.07
	Subcortical	1.69	0.09	8.15	.000*	2.19	0.03*	1.36	.000*
Scattered	AC	1.98	0.04*	1.07	0.2	1.38	0.03*	- 0.03	0.9
	PC	0.49	0.6	- 0.12	0.9	- 0.5	0.6	- 0.09	0.9
Multiple	AC unilateral	1.59	0.1	0.79	0.4	1.66	0.02*	0.42	0.6
	Bilateral AC & PC	0.32	0.7	0.28	0.7	2.03	0.09	0.16	0.8

Sig. = Significance
**= Significant*

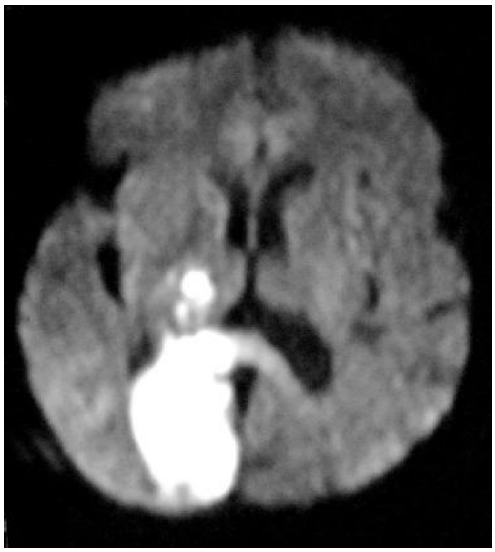


Fig. 3. Multiple lesions: Diffusion weighted MR image shows multiple lesions in more than one vascular territory

The goal of imaging in the acute phase of ischemic stroke is to identify the location and extension of the relevant lesion and the presence of significant arterial stenosis or occlusion. Multimodal MR imaging supports the achievement of these diagnostic goals, improving the accuracy of early ischemic stroke subtype identification. The various MRI patterns of acute brain ischemia (size, topography, and multiplicity) visualized using DWI are essential factors that can suggest the most likely mechanisms of origin. This information may have an impact on decisions regarding therapy and the performance of additional diagnostic tests [15].

Single cortical or subcortical hemispheric infarcts greater than 1.5 cm in diameter on brain imaging is considered to be potentially large-artery disease strokes. Supportive evidence by the vascular imagery of more than 50% stenosis in an appropriate intracranial artery (presumably due to atherosclerosis) is needed. This is in agreement with our results in which the majority of stroke patients with cortical and subcortical infarcts are due to either atherosclerosis (cortical 33.3%, subcortical 14%) or cardiac causes (cortical 44.8%, subcortical 10.4%). Rovira et al., 2005 reported that 20% of stroke in the territory of a high-grade symptomatic ICA are cardioembolic which coincides with our study(15). Atherosclerosis of the small penetrator vessels or atheromatosis is the leading cause of small-artery disease. Atheroma plaques are localized in the proximal perforating arteries (microatheroma), in the origin of the penetrator artery (junctional atheroma), or in the parent artery on the circle of Willis (mural atheroma). The small-vessel disease is the cause of about 25% of all first-ever strokes. The most frequent pathologic events related to small-vessel disease are atherosclerosis and lipohyalinosis limited to the small penetrator vessels. In this study, small vessel disease was found in subcortical infarct patients (100%) more than cortical infarction. The cardiogenic embolism is responsible for about 15–27% of all first-ever strokes. The incidence is higher in patients under 45 years old, primarily because of the lower rate of atherosclerotic disease in this age group. Our results showed that scattered lesion in the distribution of AC artery was more common (10.5%) than PC artery in which the infarct appear diffusely scattered. In the present study, multiple lesions detected on DW imaging represented more than (16.7%) of ischemic strokes, along with the course of AC more than PC and caused by atherosclerotic disease. This finding is not supported by the results of Bogousslavsky, (1996) who found a high prevalence (75%) of internal carotid artery stenosis or occlusion in patients with multiple infarcts in one hemisphere. In a consecutive study, Bogousslavsky et al. [16] reported that

large-artery disease and CE explain approximately 60% of multiple acute infarctions in the unilateral AC.

5. CONCLUSION

We concluded that there is a correlation between the ASCO stroke subtype and ischemic lesion appearance on DWI. ASCO classification for stroke subtype give us the best available information is highly flexible, and it follows the daily clinical practice. The pattern and distribution of ischemic lesions in DWI, therefore, helps in the determination of stroke etiology and hence its prevention according to ASCO stroke criteria.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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