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RESEARCH

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Clinical and prognostic significance of baseline microRNA 223 in acute ischemic stroke

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Abstract

Background Acute ischemic stroke (AIS) is the second leading cause of disability and death worldwide. Micro-RNA (miRNA)-223 was first identified as a regulator of hematopoietic lineage differentiation. Later, its diverse roles were discovered in a wide spectrum of pathological conditions. The present study aimed to assess the clinical and prognostic significance of miR-223 in patients with acute ischemic stroke (AIS). The study included 93 patients with AIS diagnosed on the basis of clinical and radiological findings. In addition, there were 50 healthy subjects who served as controls. Patients were classified into two categories: Those with favorable functional outcome (modified Rankin Scale (mRS): 0–2) and others with unfavorable functional outcome (mRS: 3–6) at 6 months post-stroke.

Results The present prospective longitudinal study included 93 patients with AIS. They included 60 males (64.5%) and 33 females (35.5%) with an age of 64.5 ± 12.4 years. At the end of 6-month follow up, 44 patients (47.3%) had favorable outcome while the remainder 49 patients (52.7%) had unfavorable outcome. Patients with favorable outcome had significantly lower baseline miR-223 levels [median (IQR): 4.4 (2.0–6.3) versus 8.4 (4.5–14.9), $p < 0.001$], lower HbA1c levels (5.6 ± 1.0 versus 6.2 ± 1.2, $p = 0.006$) and lower C-reactive protein (CRP) levels [median (IQR): 8.9 (5.1–26.7) versus 15.2 (6.2–39.3) mg/dL, $p = 0.02$]. Multivariate binary logistic regression analysis recognized high baseline miR-223 [OR (95% CI) 1.13 (1.06–1.24), $p = 0.011$], infarct size [OR (95% CI) 2.58 (1.66–4.77), $p = 0.001$] and National Institutes of Health Stroke Scale (NIHSS) [OR (95% CI) 2.11 (1.74–3.09), $p = 0.004$] as significant predictors of unfavorable outcome in the studied patients.

Conclusions Elevated baseline miR-223 levels are associated with high NIHSS and larger infarct size at baseline and can effectively predict patients' outcome at 6-months post-stroke.

Keywords Acute ischemic stroke, MicroRNAs, miR-223, National Institutes of Health Stroke Scale

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Introduction

Acute ischemic stroke (AIS) is the second leading cause of disability and death worldwide with the maximal disease burden noted in low and middle-income countries. Unfortunately, less than 5.0% of patients receive intravenous thrombolysis therapy within the effective therapeutic window [1].

Conventionally, AIS is diagnosed on the basis of imaging data derived from a variety of CT or MRI techniques. However, these modalities have many logistic and diagnostic restrictions particularly in the low-resource setting. Identification of readily available diagnostic tools is expected to improve clinical outcome [2]. In this context, many blood-based biomarkers were suggested to have diagnostic and prognostic value in AIS. The most frequently studied markers are brain natriuretic peptide, S100 calcium-binding protein B [3] and copeptin [4].

MicroRNAs (miRNAs) are small (18–22 nucleotides) non-coding RNAs. The discovery of microRNAs in 1990s revolutionary changed the paradigm of post-transcriptional gene regulation in almost all pathological conditions [5]. In AIS, microRNAs were reported to play diverse pathogenic roles. These include dysregulated lipid hemostasis, inflammatory cells recruitment within the vascular wall, control of endothelial cells behavior, proliferation and migration of vascular smooth muscle cells and regulation of atherosclerotic plaque stability [6, 7]. Moreover, microRNAs are involved in the pathogenesis of multiple AIS risk factors including diabetes mellitus, hypertension and dyslipidemia through disruption of multiple metabolic, immunologic and apoptotic pathways [8].

miRNA-223 was first identified as a regulator of hematopoietic lineage differentiation. Later, its diverse roles were discovered in a wide spectrum of pathological conditions including infectious diseases [9], cardiovascular disorders [10], inflammatory disorders [11, 12], liver and kidney diseases [13, 14], respiratory diseases [15] and miscellaneous malignant conditions [16, 17]. In the central nervous system, miRNA-223 has been linked to ischemic neural injury through targeting type 1 insulin-like growth factor receptor (IGF1R) [18]. The present study aimed to assess the clinical and prognostic significance of miR-223 in patients with AIS.

Methods

The present prospective longitudinal study protocol was approved by the local ethical committee and all patients and/or their legal guardians provided informed consent before participating in the study. The study included 93 patients with AIS diagnosed on the basis of clinical and radiological findings. Patients were excluded if they had previous episodes of AIS, associated neoplasms, active infections or immunological disorders. In addition, there were 50 age and sex-matched healthy controls.

All patients were submitted to careful history taking, sophisticated general and neurological examination, standard laboratory assessment and radiological examination using computed tomography and/or magnetic resonance imaging. At presentation, patients were assessed using the National Institutes of Health Stroke Scale (NIHSS) [19]. Functional outcome was assessed using the modified Rankin Scale (mRS) at stroke unit discharge and at 6 months after stroke. Patients were classified into two categories: Those with favorable functional outcome (modified Rankin Scale (mRS): 0–2) and others with unfavorable functional outcome (mRS: 3–6) [20]. Stroke etiology was classified using the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) criteria as large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined cause and stroke of undetermined cause [21]. Lesions sizes were ranked into (1) small lesion with a volume < 10 ml; (2) medium lesion of 10–100 ml; and (3) large lesion with a volume > 100 ml [22].

RNAs were extracted from serum using Qiagen (Valencia, CA) kits. For real-time qPCR, a MiScript SYBR Green PCR kit (Qiagen, USA) and primer sets for miR223 and mir U6 as an internal control were used (Qiagen, USA). The expression levels of microRNA-223 were identified using the Ct method.

Data obtained from the present study were expressed as mean and standard deviation (SD), median and interquartile range (IQR) or number and percent. Variables were compared using t test, Mann–Whitney U test or chi-square test as appropriate. Binary logistic regression analysis was used to identify predictors of unfavorable outcome. Receptor operator characteristic (ROC) curve analysis was used to assess the diagnostic performance of the investigated marker. All statistical operations were processed using SPSS 27 with p value less than 0.05 considered statistically significant.

Results

The present study included 93 patients with AIS. They included 60 males (64.5%) and 33 females (35.5%) with an age of 64.5 ± 12.4 years. In addition, there were 50 age and sex-matched healthy controls. Patients had significantly higher circulating miR-223 levels as compared to controls [median (IQR):5.99 [3.02–15.82] versus 1.15 (0.97–1.38) $p < 0.001$]. At the end of 6-month follow up, 44 patients (47.3%) had favorable outcome while the remainder 49 patients (52.7%) had unfavorable outcome. Comparison between patients with favorable and unfavorable outcomes revealed that the former group are significantly younger (61.7 ± 11.0 versus 70.5 ± 13.3 years,

$p < 0.001$) with significantly higher frequency of females (47.7% versus 24.5%, $p = 0.019$). Also, it was found that patients with favorable outcome had significantly lower frequency of large-sized infarcts (9.1% versus 34.7%, $p = 0.002$). In addition, it was found that patients with favorable outcome had significantly lower HbA1c levels (5.6 ± 1.0% versus 6.2 ± 1.2, $p = 0.006$), lower CRP levels [median (IQR): 8.9 mg/dL (5.1–26.7) versus 15.2 (6.2–39.3), $p = 0.02$] and lower miR-223 levels [median (IQR): 4.4 (2.0–6.3) versus 8.4 (4.5–14.9), $p < 0.001$] (Table 1).

Table 1 Clinical and laboratory findings in the studied patients in relation to discharge outcome (n = 93)

	All patients n = 93	**Favorable outcome n = 44**	**Unfavorable outcome n = 49**	**p value**
Age (years) mean ± SD	64.5 ± 12.4	61.7 ± 11.0	70.5 ± 13.3	< 0.001
Male/female n	60/33	23/21	37/12	0.019
BMI (Kg/m^2) mean ± SD	32.1 ± 6.9	31.6 ± 6.1	32.6 ± 7.6	0.48
Risk factors n (%)				
TIA	43 (46.2)	24 (54.6)	19 (38.8)	0.13
AF	8 (8.6)	1 (2.3)	7 (14.3)	0.039
Diabetes mellitus	43 (46.2)	18 (40.9)	25 (51.0)	0.33
Hypertension	58 (62.4)	27 (61.4)	31 (63.3)	0.85
Smoking	13 (14.0)	9 (20.5)	4 (8.2)	0.09
Affected side n (%)				
Right	46 (49.5)	20 (45.4)	26 (53.1)	0.46
Left	47 (50.5)	24 (54.6)	23 (46.9)	
Site n (%)				
Anterior circulation	74 (79.6)	32 (72.7)	42 (85.7)	0.11
Posterior circulation	16 (17.2)	9 (20.5)	7 (14.3)	
Both	3 (3.2)	3 (6.8)	–	
TOAST classification n (%)				
Large artery	47 (50.5)	24 (54.6)	23 (46.9)	0.76
Cardioembolic	18 (19.4)	8 (18.2)	10 (20.4)	
Small artery	28 (30.1)	12 (27.3)	16 (32.7)	
Infarct size n (%)				
Small	32 (34.4)	22 (50.0)	10 (20.4)	0.002
Medium	40 (43.0)	18 (40.9)	22 (44.9)	
Large	21 (22.6)	4 (9.1)	17 (34.7)	
NIHSS	14.3 ± 6.0	9.3 ± 3.5	18.9 ± 3.8	< 0.001
Laboratory findings mean ± SD/median (IQR)				
Hb (gm/dL)	13.5 ± 1.0	13.3 ± 1.0	13.6 ± 0.9	0.14
WBCs (× 10^3/mL)	6.5 ± 1.0	6.8 ± 1.1	6.4 ± 0.9	0.08
Platelets (× 10^3/mL)	277.6 ± 71.2	270.6 ± 80.8	283.9 ± 61.4	0.37
FBG (mg/dL)	117.6 ± 41.7	109.4 ± 31.3	124.9 ± 48.3	0.07
Cholesterol (mg/dL)	159.2 ± 32.8	163.1 ± 38.2	155.8 ± 27.0	0.29
Triglycerides (mg/dL)	138.5 ± 56.1	155.5 ± 59.8	163.2 ± 48.2	0.5
LDL (mg/dL)	85.4 ± 25.8	85.3 ± 29.2	85.6 ± 22.7	0.96
HDL (mg/dL)	46.1 ± 10.7	46.7 ± 11.4	45.6 ± 10.2	0.63
HbA1c (%)	5.9 ± 1.2	5.6 ± 1.0	6.2 ± 1.2	0.006
CRP (mg/dL)	12.9 (6.0–32.7)	8.9 (5.1–26.7)	15.2 (6.2–39.3)	0.02
Uric acid (mg/dL)	5.2 ± 1.6	4.9 ± 1.8	5.4 ± 1.4	0.18
Urea (mg/dL)	30.1 ± 10.3	28.4 ± 6.8	31.7 ± 12.5	0.11
Creatinine (mg/dL)	1.1 ± 0.4	1.0 ± 0.3	0.9 ± 0.3	0.2
miR-223	5.99 (3.02–11.16)	4.4 (2.0–6.3)	8.4 (4.5–14.9)	< 0.001

AF: Atrial fibrillation, BMI: Body mass index, CRP: C-reactive protein, FBG: Fasting blood glucose, Hb: Hemoglobin, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, miR-223: MicroRNA-223, NIHSS: National Institutes of Health Stroke Scale, TIA: Transient ischemic attack, TOAST: Trial Org 10172 classification in Acute Stroke Treatment, WBCs: White blood cells.

Spearman's correlation analysis identified significant correlation between miR-223 levels and infarct size (r = 0.35, p < 0.001), NIHSS (r = 0.29, p = 0.004), cholesterol levels (r = 0.23, p = 0.03), HDL (r = -0.33, p = 0.001) and CRP levels (r = 0.27, p = 0.001) in all patients (Table 2). Multivariate binary logistic regression analysis recognized infarct size [OR (95% CI): 2.58 (1.66–4.77), p = 0.001], NIHSS [OR (95% CI): 2.11 (1.74–3.09), p = 0.004] and miR-223 [OR (95% CI): 1.13 (1.06–1.24), p = 0.011] as significant predictors of unfavorable outcome in the studied patients (Table 3). ROC curve analysis showed good performance of miR-223 in distinguishing patients with favorable outcome from their counterparts with unfavorable outcome [Cut-off: 6.56, AUC: 0.713, sensitivity: 71.4%, specificity: 79.5%] (Fig. 1).

Discussion

The present study found that circulating baseline miR-223 levels are significantly increased in AIS patients as compared to healthy controls. Moreover, the study identified a relation between elevated miR-223 levels and NIHSS scores, stroke volume and unfavorable outcome at 6 months. These findings with consistent with the study of Wang and colleagues [23] who noted that miR-223 levels within 72 h after stroke are elevated in AIS patients in comparison to controls. The study of Chen

Table 2 Correlation between baseline mir-223 levels and clinical and laboratory data

	All patients		Patients with favorable outcome		Patients with unfavorable outcome	
	r	p	r	p	r	p
Age	0.12	0.23	− 0.15	0.32	0.08	0.61
BMI	0.002	0.99	− 0.04	0.78	− 0.14	0.33
Infarct size	0.35	< 0.001	0.12	0.44	0.19	0.19
NIHSS	0.29	0.004	0.16	0.3	− 0.09	0.53
Hb	0.03	0.77	− 0.02	0.88	− 0.03	0.85
WBCs	− 0.02	0.88	− 0.01	0.93	− 0.05	0.72
Platelets	− 0.01	0.92	− 0.03	0.83	− 0.12	0.41
FBG	0.04	0.72	0.12	0.46	− 0.02	0.87
Cholesterol	0.23	0.03	0.36	0.017	0.001	0.99
Triglycerides	0.16	0.13	0.26	0.09	− 0.06	0.66
LDL	0.18	0.09	0.4	0.008	0.01	0.92
HDL	− 0.33	0.001	− 0.48	0.001	− 0.21	0.15
HbA1c	0.01	0.91	− 0.24	0.12	− 0.05	0.74
CRP	0.27	0.001	0.11	0.44	0.17	0.24
Uric acid	− 0.02	0.84	0.002	0.99	− 0.27	0.058
Urea	0.11	0.3	0.25	0.1	− 0.009	0.95
Creatinine	0.09	0.37	0.11	0.47	0.13	0.39

BMI: Body mass index, CRP: C-reactive protein, FBG: Fasting blood glucose, Hb: Hemoglobin, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, NIHSS: National Institutes of Health Stroke Scale, WBCs: White blood cells

Table 3 Predictors of unfavorable outcome at 6 months in the studied patients

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p value	OR	95% CI	p value
Age	1.062	1.022–1.1	0.002	0.93	0.84–1.04	0.43
Sex	2.82	1.17–6.79	0.021	1.14	0.98–3.41	0.37
Size	2.99	1.59–5.62	< 0.001	2.58	1.66–4.77	0.001
NIHSS	2.26	1.54–3.32	< 0.001	2.11	1.74–3.09	0.004
CRP	1.027	1.003–1.053	0.03	0.98	0.94–1.041	0.29
miR223	1.18	1.072–1.3	< 0.001	1.13	1.06–1.24	0.011

CRP: C-reactive protein, miR-223: MicroRNA-223, NIHSS: National Institutes of Health Stroke Scale

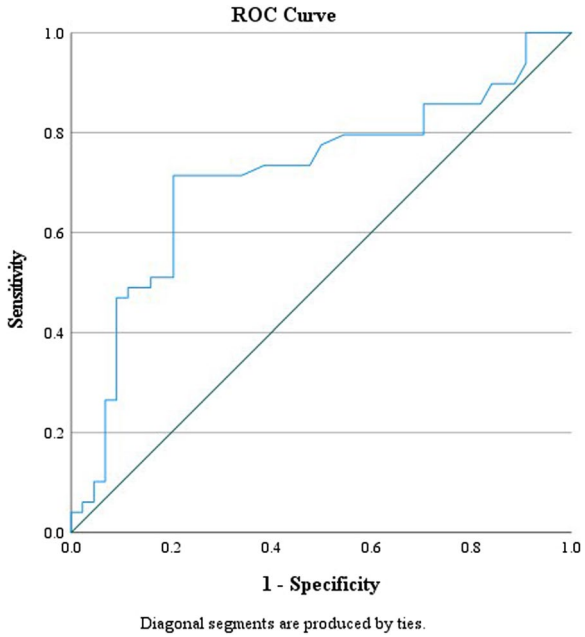

Fig. 1 ROC curve for miR-223 and outcome

and colleagues [24] additionally identified an association between elevated miR-223 levels and poor short-term outcomes. Likewise, it was found that diabetic patients with AIS had significantly higher miR-223 levels in plasma [25] and peripheral blood mononuclear cells [26] when compared with their counterparts without stroke. Results of the present study are also supported by the experimental work of Voelz and colleagues [27] who noted increased cortical and serum expression of miR-223-3p after transient middle cerebral artery occlusion in rats. In contradiction with these results, the experimental work of Harraz and colleagues [28] suggested that miR-223 may play a neuroprotective role in ischemic brain injury through downregulation of glutamate receptor subunits (GluR2) with subsequent inhibition of N-methyl-d-aspartate (NMDA)-induced calcium influx into hippocampal neurons which aggravates neuronal death after ischemia.

The effects exerted by overexpression of miR-223 in AIS patients can be explained by multiple mechanisms. It was noted that platelets-induced miR-223 is responsible for enhancement of vascular endothelial cell apoptosis in stroke patients through targeting insulin-like growth factor 1 receptor [29]. In another experimental study on ischemic brain extract, it was reported that miR-223 overexpression resulted in suppression of IκB kinase alpha which enhances cellular response to inflammation [30]. Moreover, it was found that miR-223 inhibited proliferation of cortical neurons by inhibition of type 1 insulin-like growth factor receptor expression [18].

Results of the present study may have useful therapeutic implications. In one study, it was shown that use of anti-miR-223-5p was associated with better expression the K+-dependent Na+/Ca2+exchanger and NCKX2 known for its neuroprotective functions [31]. It was also demonstrated that electropuncture could reduce experimental ischemic brain injury through inhibition of the miR-223/Nod-like receptor Pyrin Domain Containing 3 (NLRP3) pathway [32].

In another experimental work using in-vitro cell model and middle cerebral artery occlusion in-vivo rat model, it was found that reduced ribosomal protein L34-antisense RNA1 (RPL34-AS1) was associated with more brain damage in IS model. Its neuroprotective effects are reversed by miR-223-3p and it is thought it can be used as a therapeutic target in ischemic stroke via regulation of the 223-3p/insulin-like growth factor 1 receptor axis [33].

Conclusions

In conclusion, higher miR-223 levels are associated with high NIHSS and infarct size at baseline and can effectively predict patients' outcome at 6-months post-stroke. However, these conclusions may be limited by the relatively small sample size and the short duration of follow up.

Abbreviations

AF	Atrial fibrillation
AIS	Acute ischemic stroke
BMI	Body mass index
CRP	C-reactive protein
FBG	Fasting blood glucose
Hb	Hemoglobin
HDL	High-density lipoprotein
IGF1R	Insulin-like growth factor receptor
IQR	Interquartile range
LDL	Low-density lipoprotein
mRS	Modified Rankin Scale
miRNAs	MicroRNAs
NIHSS	National Institutes of Health Stroke Scale
TIA	Transient ischemic attack
TOAST	Trial Org 10,172 classification in Acute Stroke Treatment
WBCs	White blood cells

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Author contributions

Conceived and designed the experiments: REMA, WAE, FME, SAK, RSA, AEE enrolled the patients: FGY, MAAR Performed the experiments: SMA, ARM data management and analysis, FGY, MAAR: reagents/materials/analysis tools: FGY, MAAR:, prepared the manuscript: SMA, ARM, read and approve the manuscripts: REMA, WAE, FME, SAK, RSA, AEE. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the ethical committee of Al-Azhar University Faculty of Medicine on 29/8/2023. Informed written consent was obtained from all the patients enrolled in this study.

Informed consent
Written informed consent was obtained from all patients or their legal guardians before enrollment in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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