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Egypt J Neurol Psychiatry Neurosurg (2021) 57:111
https://doi.org/10.1186/s41983-021-00364-7

The Egyptian Journal of Neurology, Psychiatry and Neurosurgery

RESEARCH Open Access

Paradoxical role of hepatocyte growth factor in ischemic stroke: stroke risk/stroke recovery

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Abstract

Background: Hepatocyte growth factor (HGF) has an obvious pathological role in atherosclerosis and plaque instability leading to an acute ischemic stroke; however, its beneficial role in stroke recovery is still restricted to experimental studies. The aim of the current study was to investigate the association between HGF and carotid atherosclerosis and evaluate its value as a prognostic marker of ischemic stroke and its role in stroke recovery.

Results: This case–control study was done on 100 patients with first time anterior circulation ischemic stroke, subjected to clinical and laboratory evaluation of atherosclerosis risk factors. Brain imaging, cardiac work-up and ultrasonographic assessment of carotid atherosclerosis (using intimal medial thickness and plaque score) were all done. Clinical evaluation of initial stroke severity, using National Institutes of Health Stroke Scale (NIHSS), and stroke outcome after 3 m, using Modified Rankin Scale (MRS), was performed. Measurement of HGF serum concentration was done to all stroke patients within 24 h of stroke onset and compared to results of 100 matched healthy subjects aged more than 50 years. HGF was significantly higher in stroke patients than healthy controls and in atherothrombotic than cardioembolic stroke group and its level was significantly correlated with atherosclerosis risk factors, degree of carotid atherosclerosis and better stroke outcome; however, it was not significantly correlated with initial stroke severity.

Conclusion: HGF is strongly associated with carotid atherosclerosis and other atherosclerosis risk factors and subsequent atherothrombotic stroke. Also, it can be used as a good prognostic marker in atherothrombotic stroke suggesting its role in stroke recovery but more studies are needed to explore this beneficial role as well as its therapeutic potentials in ischemic stroke patients.

Keywords: Hepatocyte growth factor, Ischemic stroke, Atherosclerosis, Prognosis

Background

Hepatocyte growth factor (HGF), initially described as a mitogen for hepatocytes, is a potent angiogenic factor and endothelium-specific growth factor that affects a wide range of tissues [1, 2]. Previous data in humans have demonstrated expression of HGF and its receptor c-Met in atherosclerotic plaques [3]. So, it is hypothesized that HGF may play a role in the natural history of atherosclerosis and hence the pathogenesis of cerebrovascular disease, including ischemic stroke [4, 5]. High HGF levels, within atherosclerotic plaques, may lead to plaque neovascularization [3, 6], which in turn, facilitates infiltration of leukocytes and inflammatory stimuli. Subsequently these changes further enhance angiogenesis in atherosclerotic lesions with further plaque instability and plaque rupture leading to an acute ischemic stroke [7, 8]. It is unclear whether high HGF levels are a risk factor for ischemic stroke or a result of it, and whether HGF is an independent risk factor for stroke or merely a marker for other cardiovascular diseases (CVD) risk factors.

On the other hand, HGF was described as a neuroprotector and angiogenesis promoter after cerebrovascular accidents [9]. It was found that HGF levels in the

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acute stroke phase correlate closely with clinical recovery in the post-acute stroke phase, by inducing long-term neuroprotection lasting beyond the discontinuation of treatment, translating into enhanced motor coordination recovery suggesting that HGF induces favorable responses in the brain tissue that facilitate brain remodeling, and these unique features make it a promising agent for stroke treatment [10, 11].

To address these two contradictory issues, we conducted the present study to investigate the correlation between HGF and acute ischemic stroke, stroke severity, stroke subtype (atherothrombotic versus cardioembolic), carotid atherosclerosis and other atherosclerotic risk factors, also to evaluate its prognostic value and role in stroke recovery, opening road for exploring its therapeutic potentials in acute stroke.

Methods

This study was conducted on 100 first time anterior circulation acute ischemic stroke patients, within 24 h of stroke onset, 49 males and 51 females, aged more than 50 years, enrolled from our hospital between May 2017 and May 2018. Patients were matched with 100 healthy subjects (who do not have risk factors like diabetes, hypertension, smoking, dyslipidemia) aged more than 50 years recruited form outpatient clinics.

All 100 stroke patients included in this study were subjected to thorough history taking, complete general and neurological examinations, body mass index (BMI) calculation [BMI = weight (kg)/height (m^2)] and obesity was defined as: BMI > 25 kg/m^2 [12], assessment of stroke severity using National Institutes of Health Stroke Scale (NIHSS), and routine laboratory measurements including fasting blood sugar, fasting lipid profile, serum creatinine, liver function tests and cardiac enzymes (CK-MB, Troponin I).

High-resolution B-mode ultrasound color Doppler, and pulse Doppler ultrasonography of both carotid arteries were performed to all patients using (SONOS 5500; Hewlett Packard, USA) with linear transducer 10 MHz array probe with measuring of intima–media thickness (IMT) and plaque score (PS). Carotid IMT was measured as the distance from the leading edge of the first echogenic line (lumen–intima interface) to the leading edge of the second echogenic line (media–adventitia interface). Mean (IMT) is calculated by measuring the mean of the IMT of right and left common carotid artery (CCA). Carotid atherosclerosis was defined as carotid intima–media thickness IMT > 0.8 mm [13]. Plaque was defined as: the presence of wall thickness of at least 50% greater than the thickness of the surrounding wall [12], or a protrusion into the lumen. Carotid atherosclerosis was classified as either mild [IMT 0.9–1 mm], moderate (IMT 1.1–1.9 mm) and severe (IMT ≥ 2 mm) [14]. Plaque score (PS) was calculated as the sum of the thickness of all the plaques in both carotid arteries [5, 15]. Carotid plaque burden was classified according to plaque score (PS) into normal (score 0), mild (score 1–5), moderate (score 5.1–10), and severe (score over 10) [16]. Three months after the onset of stroke, the functional outcome of stroke was assessed by Modified Rankin Scale (MRS) done by senior neurologist in the outpatient clinic follow-up visit. Brain imaging [either computed tomography (CT) or magnetic resonance imaging (MRI)], electrocardiography (ECG), Holter and echocardiograph examination were performed to all patients included in this study.

Measurement of serum HGF concentrations done to all stroke patients and control group. Samples were collected within 24 h from stroke onset. HGF concentration in the serum was determined using an enzyme-linked immunosorbent assay kit for human HGF (Human HGF instant ELISA BMS2069INST, Affymetrix eBioscience, Vienna, Austria). The interassay and intra-assay coefficients for this assay were 8.3% and 7.6%, respectively. The reference range reported by the manufacturer was < 0.390 ng/ml.

Depending on results of brain imaging, cardiac work-up and carotid ultrasound, stroke patients were divided into two groups: 50 patients with carotid atherosclerosis without cardiac source (atherothrombotic) and 50 patients with cardiac source of the stroke (atrial fibrillation; AF) without carotid atherosclerosis (cardioembolic).

Patients were excluded if they have previous stroke (hemorrhagic or ischemic), transient ischemic attack (TIA), brain tumor, demyelinating disease or CNS infection, chronic liver or renal diseases. Posterior circulation strokes were also excluded as usefulness of duplex ultrasonography (DUS) for screening of extracranial vertebral artery stenosis or visualization of atherosclerosis is limited [17].

The study was performed in accordance with the Declaration of Helsinki and approved by the local ethical committee and informed verbal consent was obtained from all subjects before the study was commenced after fully explaining the study and its aims to them.

Statistical analysis

Statistical analysis was conducted by Statistical package of Social Science (SPSS) version 20 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). Quantitative data were expressed as mean and standard deviations ($X \pm SD$) and analyzed applying Student *t*-test. The Mann–Whitney *U* and Kruskal–Wallis *H* test were used to allow the comparison of two or more independent groups. $P < 0.05$ was determined as statistically significant, whereas *P* value < 0.001 was considered to be highly statistically

significant, on the other hand P value > 0.05 was considered statistically not significant. Statistical correlations using Spearman's correlation coefficient, (ρ, also signified by rs) used to measure the strength and direction of association between ranked variables.

Results

The clinical parameters of all patients and controls are presented in Table 1, which shows no difference in age and sex distribution among cases and control groups.

On comparing between atherothrombotic and cardioembolic stroke groups, all vascular risk factors were distributed more in atherothrombotic than the cardioembolic group (Table 2), also degree of carotid atherosclerosis measures by IMT and carotid plaque burden measured by PS were statistically significantly higher in the atherothrombotic group (Tables 3, 4). There was no difference between both groups in the initial stroke severity assessed by NIHSS (Table 5), however the stroke outcome after 3 months measures by MRS was better in atherothrombotic group than cardioembolic with statistically significant difference (Table 6).

The mean serum concentration of HGF in stroke patients group was statistically significant higher than that of the control group (Table 7) and in the atherothrombotic stroke group than cardioembolic ones (Table 8), and in those with vascular risk factors for atherosclerosis (smoking, obesity, dyslipidemia, DM and hypertension) than those without (Table 9). Also it was directly related to the increase in age of stroke patients in a statistically significant way (Table 10) and the degree of atherosclerosis either by IMT or the carotid plaque score burden (Tables 11, 12), but not with sex or initial stroke severity assessed by (NIHSS) (Table 13).

On the other hand, we find a significant correlation between higher HGF levels and lesser functional disability after 3-month measures by MRS indicating better prognosis (Tables 14, 15).

Discussion

In the current study, HGF concentration was significantly higher in stroke patients than control and in atherothrombotic stroke than cardioembolic ones. These results were matched with many studies [18–21], who reported an increase of HGF in the very early stage of ischemic stroke and it decreases as the disease evolves, suggesting that thrombus formation abated. So they suggested that circulating HGF is a reliable early marker of cerebral infarction, its assay may be useful for diagnosing cerebral thrombosis. HGF might be released from the vessel wall by unknown mechanisms related to endothelial damage mediated by thrombus formation

Table 1 Age and sex distribution among cases and control groups

	The studied groups				Test	*P* value
	Patients $N=100$		Control $N=100$			
Age						
$X \pm SD$	71.42 ± 9.37		70.30 ± 9.17		0.85	0.38
Range	51–85		51–85			
	No	%	No	%	X^2	
Sex						
Male	49	49	54	54	0.5	0.48
Female	51	51	46	46		

X mean, *SD* standard deviation, X^2 Chi-square test

Table 2 Vascular risk factors for atherosclerosis among patients group

	The patient group (100 stroke patients)					
	Carotid atherosclerosis $N=50$		Cardioembolic $N=50$		Total $N=100$	
	No	%	No	%	No	%
Smoking	27	54	5	10	32	32
Obesity	43	86	16	32	59	59
DM	42	84	11	22	53	53
Dyslipidemia	37	74	11	22	48	48
Hypertension	37	74	30	60	67	67

Table 3 Carotid intima–media thickness (IMT) among atherosclerotic and cardioembolic groups

	The patient group						Test *U*	*P* value
	Carotid atherosclerosis *N* = 50		Cardioembolic *N* = 50		Total *N* = 100			
IMT								
X ± SD	2.27 ± 1.26		0.60 ± 0.14		1.44 ± 1.22		8.6	< 0.001*
Range	0.90–5		0.3–0.80		0.3–5			
	No	%	No	%			X^2	
Atherosclerosis severity								
No (IMT ≤ 0.8 mm)	0	0	50	100	50	50	100	< 0.001*
Mild (IMT 0.9–1 mm)	11	22	0	0	11	11		
Moderate (IMT 1.1–1.9 mm)	17	34	0	0	17	17		
Severe (IMT ≥ 2 mm)	22	44	0	0	22	22		

X mean, *SD* standard deviation, X^2 Chi-square test, *U* Mann–Whitney *U*, *highly significant, *IMT* intimal medial thickness

Table 4 Carotid plaque burden among atherosclerotic and cardioembolic groups

	The patient group						Test *U*	*P* value
	Carotid atherosclerosis *N* = 50		Cardioembolic *N* = 50		Total *N* = 100			
Number of plaques								
X ± SD	7.16 ± 5.23		0.0 ± 0.0		3.58 ± 5.15		8.4	< 0.001
Range	0–17		0–0		0–17			
	No	%	No	%			X^2	
Plaque burden								
No plaques	6	12.0	50	100	56	56	78.6	< 0.001
Mild	14	28.0	0	0	14	14		
Moderate	10	20.0	0	0	10	10		
Severe	20	40.0	0	0	20	20		

X mean, *SD* standard deviation, X^2 Chi-square test, *U* Mann–Whitney *U*, *highly significant

Table 5 National Institutes of Health Stroke Scale (NIHSS) among patients group

	The patient group (100 stroke patients)						Test	*P* value
	Carotid atherosclerosis *N* = 50		Cardioembolic *N* = 50		Total *N* = 100			
NIHSS								
X ± SD	12.64 ± 9.89		13.88 ± 8.61		13.26 ± 9.24		0.69	0.49
Range	1–40		1–35		1–40			
	No	%	No	%			X^2	
NIHSS								
Minor impairment	15	30	11	22	26	26	2.10	0.55
Moderate	13	26	13	26	26	26		
Moderate-to-severe	11	22	17	34	28	28		
Severe impairment	11	22	9	18	20	20		

X mean, *SD* standard deviation, X^2 Chi-square test

Table 6 Modified Rankin Scale (MRS) among patients group

	The patient group (100 stroke patients)						Test	*P* value
	Carotid atherosclerosis *N* = 50		Cardioembolic *N* = 50		Total *N* = 100			
	No	%	No	%			X^2	
MRS								
0	5	10	0	0	5	5	77.2	< 0.001*
1	10	20	2	4	12	12		
2	12	24	1	2	13	13		
3	8	16	3	6	11	11		
4	15	30	1	2	16	16		
5	0	0	39	78	39	39		
6	0	0	4	8	4	4		

X^2 Chi-square test, *MRS* Modified Rankin Scale, *highly significant

Table 7 HGF concentration in patients and control groups

	The studied groups		*U* test	*P* value
	Patients *N* = 100	Control *N* = 100		
HGF Conc. (ng/ml)				
X ± SD	0.52 ± 0.18	0.26 ± 0.08	9.83	< 0.001*
Range	0.15–0.85	0.12–0.39		

X mean, *SD* standard deviation, *U* Mann–Whitney *U* test, *highly significant, *HGF* hepatocyte growth factor

Table 8 HGF concentration in atherothrombotic and cardioembolic groups

	The patient group		*t*-test	*P* value
	Atherothrombotic (*N* = 50)	Cardioembolic (*N* = 50)		
HGF Conc. (ng/ml)				
X ± SD	0.62 ± 0.19	0.41 ± 0.09	6.88	< 0.001*
Range	0.17–0.85	0.15–0.50		

X mean, *SD* standard deviation, *highly significant, *HGF* hepatocyte growth factor

[19]. Moreover, in a multi-ethnic study investigating the association of circulating HGF with incident stroke done by Bell and colleagues, they concluded that circulating HGF was positively associated with the incidence of stroke in a diverse, population-based cohort of both sexes from the United States especially with ischemic stroke because there were few hemorrhagic strokes. Their findings support the hypothesis that circulating HGF is a marker of endothelial damage and suggest that HGF may have utility as a prognostic marker of stroke risk [22].

We also found that HFG correlate with degree of carotid atherosclerosis and plaque burden and other

Table 9 The concentration of HGF level in stroke patients with and without vascular risk factors

Stroke patients (*N* = 100)	HGF Concentration (ng/ml)		*U* test	*P* value
	X ± SD	Range		
Hypertensive (*N* = 67)	0.59 ± 0.14	0.4–0.85	6.24	< 0.001*
Non-hypertensive (*N* = 33)	0.37 ± 0.17	0.15–0.82		
Diabetic (*N* = 67)	0.62 ± 0.17	0.23–0.85	6.24	< 0.001*
Non-diabetics (*N* = 33)	0.40 ± 0.11	0.15–0.54		
Smoker (*N* = 32)	0.72 ± 0.07	0.60–0.85	7.83	< 0.001*
Non-smoker (*N* = 68)	0.42 ± 0.12	0.15–0.82		
Dyslipidemic (*N* = 48)	0.61 ± 0.18	0.43 ± 0.12	5.07	< 0.001*
Non-dyslipidemic (*N* = 52)	0.17–0.83	0.15–0.85		
Obese (*N* = 59)	0.60 ± 0.15	0.23–0.83	5.90	< 0.001*
Non-obese (*N* = 41)	0.39 ± 0.13	0.15–0.82		

X mean, *SD* standard deviation, *U* Mann–Whitney *U* test, *highly significant, *HGF* hepatocyte growth factor

Table 10 HGF concentration in different age groups of stroke patients

	The patient group (100 stroke patients)			*K* test	*P* value
	Age group (50–65 years)	Age group (66–80 years)	Age group (≥ 81 years)		
HGF					
X ± SD	0.33 ± 0.12	0.50 ± 0.10	0.74 ± 0.12	58.5	< 0.001*
Range	0.15–0.50	0.25–70	0.21–0.85		

X mean, *SD* standard deviation, *K* Kruskal–Wallis test, *highly significant, *HGF* hepatocyte growth factor

Table 11 The relation between HGF concentration and the degree of carotid atherosclerosis according to (IMT)

	Severity of atherosclerosis				*K* test (*P* value)
	No (IMT ≤ 0.8 mm)	Mild (IMT 0.9–1 mm)	Moderate (IMT 1.1–1.9 mm)	Severe (IMT ≥ 2 mm)	
HGFconc. (ng/ml)					
X ± SD	0.41 ± 0.09	0.32 ± 0.15	0.61 ± 0.04	0.77 ± 0.04	75.4
Range	0.15–0.50	0.17–0.59	0.54–0.70	0.71–0.85	(< 0.001)*

X mean, *SD* standard deviation, *K* Kruskal–Wallis test, *highly significant, *HGF* hepatocyte growth factor, *IMT* intimal medial thickness

Table 12 The relation between HGF concentration and the carotid plaque burden measured by PS

	Carotid plaque burden (plaque score) (PS)				*K* test (*P* value)
	No plaques (score 0)	Mild (score 1–5)	Moderate (score 5.1 10)	Severe (score > 10)	
HGFconc. (ng/ml)					
X ± SD	0.42 ± 0.11	0.45 ± 0.16	0.67 ± 0.06	0.76 ± 0.04	63.2
Range	0.15–70	0.17–0.60	0.61–0.80	0.71–0.85	(< 0.001)*

X mean, *SD* standard deviation, *K* Kruskal–Wallis test, *highly significant, *HGF* hepatocyte growth factor, *PS* plaque score

Table 13 The relation between HGF concentration and stroke severity assessed by NIHSS

	NIHSS				
	Minor impairment *N* = 26	Moderate impairment *N* = 26	Moderate-to–severe impairment *N* = 28	Severe impairment *N* = 20	*K* test (*P* value)
HGFconc. (ng/ml)					
X ± SD	0.52 ± 0.19	0.52 ± 0.16	0.52 ± 0.18	0.49 ± 0.18	0.31
Range	0.20–0.80	0.17–0.77	0.15–0.83	0.21–0.85	(0.96)

X mean, *SD* standard deviation, *K* Kruskal–Wallis test, *HGF* hepatocyte growth factor, *NIHSS* National Institutes of Health Stroke Scale

Table 14 Relationship between HGF and MRS among patient group

	HGF among patient group *N* = 100		*K* test	*P* value
	X ± SD	Range		
MRS				
0	0.75 ± 0.04	0.71–0.80	32.5	< 0.001*
1	0.63 ± 0.22	0.17–0.83		
2	0.61 ± 0.26	0.21 ± 0.85		
3	0.56 ± 0.14	0.21–0.70		
4	0.49 ± 0.14	0.20–0.63		
5	0.42 ± 0.08	0.15–0.50		
6	0.40 ± 0.10	0.25–0.47		

X mean, *SD* standard deviation, *MRS* Modified Rankin Scale, *HGF* hepatocyte growth factor, *significant

Table 15 Spearman correlation between HGF and MRS

	HGF among patient group	
	r	*P* value
MRS	− 0.52	< 0.001*

MRS Modified Rankin Scale, *HGF* hepatocyte growth factor, *highly significant

atherosclerosis risk factors. These results were matched with the results of previous studies [5, 23, 24].

The role of HGF in the development of carotid atherosclerosis could be proved by the fact that HGF and c-Met are expressed in the atherosclerotic vessel wall and in plaque, but not in normal vessels, as demonstrated by immunohistochemical analysis of human carotid artery sections [3, 25, 26], and that HGF production has been induced, in cultured vascular smooth muscle cells (VSMC), by the proinflammatory mediators interleukin

1 (IL-1) and tumor necrosis factor alpha (TNF-a), both of which have been found in atherosclerotic plaques and also by low-density lipoprotein (LDL) which is a potent proatherogenic agent [25].

These results imply that serum HGF is a useful marker of carotid atherosclerosis and subsequent liability to cause thrombo-embolic stroke and also to differentiate patients with asymptomatic carotid disease who are at risk of plaque instability, who would benefit more from carotid surgery. Another possible clinical implication of this proatherogenic role of HGF is to question whether the plaque stabilization could be achieved by local therapies [27] delivered through stent- or catheter to eliminate neovascularization in a clinical setting, limiting potential systemic side effects of any therapeutic agents.

On the other end, in our study, we found a significant correlation between high HGF level and better functional outcome assessed by MRS, indicating that HGF could be used as a marker for good prognosis and enhanced recovery after ischemic stroke. Also on the experimental aspect, many studies demonstrated a clear beneficial effect of HGF in ischemic stroke model. HGF and c-Met/HGF have been reported to be upregulated mainly in the peri-infarct region as long as 28 days after permanent middle cerebral artery occlusion (MCAo), with subsequent increase in microvessels only in the peri-infarct region but not in normal regions [28] and thought to protect neurons or promote angiogenesis after cerebral ischemia.

The role of HGF in recovery of stroke was not only related to the acute stage, but extended to the chronic stage of cerebral infarction, as noted by Shimamura and colleagues, 2006, who demonstrated that HGF gene therapy delayed for as long as 7 days, improved cognitive function from ischemic stroke in the chronic stage of MCAo through reconstitution of the neuronal network [29].

On the contrary, in a study done by Zhu and colleagues, they found that serum HGF levels were higher in more severe stroke at baseline, and elevated HGF levels were probably associated with a 3-month poor prognosis independently of stroke severity among ischemic stroke patients, especially in those without heparin pretreatment [30]. They explained it by its pathological role in plaque progression and instability and greater degree of baseline endothelial dysfunction [20] with subsequent infarct expansion and hemorrhagic transformation [31]. This conclusion was supported by recent study by Zhao and colleagues; they found that soluble interleukin-2 receptors (sIL-2R) and HGF associated with unfavorable outcomes at 3 months after acute ischemic stroke [32].

The improvement in functional recovery in ischemic stroke could be based on two main properties of HGF, neuroprotection and angiogenesis. An ideal therapeutic approach to treat ischemia might have both aspects of enhancement of collateral formation (therapeutic angiogenesis) and prevention of neuronal death. HGF enhances angiogenesis in the ischemic penumbra, improves microcirculation, and inhibits destruction of the blood–brain barrier so reduce cerebral edema [33]. Moreover, HGF exerts a neuroprotective effect after cerebral ischemia by delaying neuronal death and prevention of gliosis through markedly inhibiting the proliferation and migration of astrocytes in the formation process of glial scarring by the sphingosine-1-phosphate pathway, which is closely related to cell proliferation [29, 34]. In conclusion, HGF has therapeutic potential against cerebral ischemia. Binding to the receptor c-Met, downstream signaling pathways are phosphorylated and activated, including the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), Ras/mitogen-activated protein kinase (MAPK) and signal transducer and activator of transcription (STAT) pathways, and then HGF is capable of regulating angiogenesis, glial scar formation, neurogenesis and anti-apoptosis, protecting the brain from ischemic insults [34].

The implications of this neuroprotective, angiogenic and antigliotic role of HGF were expanded to include both spinal cord and peripheral nerves. In a study done by Kitamura and colleagues, the intrathecal rhHGF preserved the corticospinal fibers and myelinated areas, thereby promoting functional recovery and magnetic resonance imaging showed significant preservation of the intact spinal cord parenchyma [35]. Furthermore, in cell-based therapeutic interventions, HGF was found to promote the survival, neuronal differentiation, and synapse formation of the grafted neural stem cells in the damaged spinal cord contributing to the better functional recovery [36]. As for peripheral nerve injury, its role was proved in animals in a study done by Boldyreva and colleagues who found that treatment by gene therapy with HGF-bearing plasmid (pC4W-hHGF) led to restoration of nerve structure and functional recovery [37].

This obviously well-known profitable role of HGF in neuronal recovery can be clinically implicated as a prognostic tool after stroke and encourage more experiments and clinical trials to study its therapeutic potentials in acute stroke.

Conclusion

HGF is significantly correlated with the severity of carotid atherosclerosis graded by (IMT and PS) and plaque instability with subsequent liability to cause thrombo-embolic stroke, on the other hand, HGF level correlate well with better functional outcome after stroke. Further studies in larger numbers of patients seem warranted to further

define the role of increased HGF in the pathogenesis of cerebral infarction, the diagnostic and prognosis power of this new laboratory test; as well as, its therapeutic potentials in acute stroke to enhance recovery.

Abbreviations
HGF: Hepatocyte growth factor; NIHSS: National Institutes of Health Stroke Scale; MRS: Modified Rankin Scale; CVD: Cardiovascular diseases; BMI: Body mass index; IMT: Intima–media thickness; PS: Plaque score; CCA: Common carotid artery; AF: Atrial fibrillation; TIA: Transient ischemic attack; CNS: Central nervous system; DUS: Duplex ultrasonography; SF: Scatter factor; VSMC: Vascular smooth muscle cells; MCAo: Middle cerebral artery occlusion; PI3K/Akt: Phosphoinositide 3-kinase/protein kinase B; MAPK: Mitogen-activated protein kinase; STAT: Signal transducer and activator of transcription pathway; pC4W-hHGF: Gene therapy with HGF-bearing plasmid.

Acknowledgements
Not applicable.

Authors' contributions
IA study design, literature review, data acquisition, manuscript preparation. NM study design, data acquisition and analysis, manuscript preparation. H. E.: literature search, data acquisition and analysis, manuscript preparation and editing. All authors have read and approved the manuscript.

Funding
This work has not received any governmental or non-governmental funds.

Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was performed in accordance with the Declaration of Helsinki and approved by the ethical committee of Menoufiya Faculty of Medicine in December, 2015. Committee's reference number is not applicable. Written Informed consent was obtained from parents, and informed assent was obtained from the children before the collection of data. Data and headache diaries for patients were obtained from the patients or their parents

Consent for publication
Not applicable

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

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Received: 6 February 2021 Accepted: 31 July 2021
Published online: 21 August 2021

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