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Original Article

The correlations of HGF expression and cognitive functions in acute ischemic stroke with brain CT perfusion imaging characteristics

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Abstract: Objective: To investigate the expressions of hepatocyte growth factor (HGF) and changes in cognitive functions in patients with acute ischemic stroke and their correlations with brain computed tomography perfusion imaging (CTPI) parameters. Methods: A total of 54 patients with acute ischemic stroke were enrolled. A biochemistry analyzer was applied to determine the HGF expressions, and the cognitive functions were evaluated using the Mini-Mental State Examination (MMSE). Brain CTPI examinations were performed on the patients. Statistical Product and Service Solutions (SPSS) 17.0 was utilized for the statistical analysis, two-sample *t*-tests were conducted for the inter-group comparisons, and Pearson correlation analyses were carried out for the relevant analyses. $P<0.05$ indicated that the difference was statistically significant. Results: The HGF expression levels in the acute ischemic stroke group were higher than they were in the normal control group. The total MMSE score in the acute ischemic stroke group was lower than it was in the normal control group. The HGF expression level was negatively correlated with cerebral blood flow (CBF), cerebral blood volume (CBV), and positive enhancement (PE), but it was positively correlated with mean transit time (MTT) and time to peak (TTP). The MMSE score had negative correlations with CBF, CBV and PE, but it was positively correlated with MTT and TTP. Conclusion: In acute ischemic stroke, the HGF expression and cognitive functions are associated with CTPI characteristics, and HGF can serve as a potential early diagnosis index for the disease.

Keywords: Acute ischemic stroke, hepatocyte growth factor, cognitive functions, brain CT perfusion imaging

Introduction

Stroke is a type of acute cerebrovascular disease with high disability and fatality rates, and it ranks third among the most common causes of death in Western countries [1]. According to data from the World Health Organization, stroke is one of the most common causes of death in China [2]. There are approximately 2.4 million cases of new-onset or recurrent stroke every year, and nearly 1.1 million people die from the disease. Among the patients with acute stroke, most (about 75%) suffer from ischemic stroke. As the proportion of the aged population increases, the burden of stroke may rise accordingly in China.

Ischemic stroke occurs when the blood flow in the brain is interrupted, which is generally triggered by thrombus or embolism. Currently, the treatment of ischemic stroke is only limited to thrombolytic therapy and symptomatic treatment [3]. A sudden interruption of blood flow in the brain leads to cell necrosis in the core region of the ischemia and subsequent cerebral edema, followed by the destruction of the blood-brain barrier [4]. The release of necrotic cells can induce apoptosis and inflammatory cytokines, cause death of half of the cells around the infarction, and aggravate brain injury. Multiple complex factors can result in the destruction of the blood-brain barrier after ischemic stroke, further exacerbating the brain injury, such as oxidative stress, the toxicity of excitatory amino acids, an excess of calcium ions, cell apoptosis, and inflammation [5, 6].

Hepatocyte growth factor (HGF) and its receptor c-Met are produced by tissue injury, and

they play a role in the tissue repair mechanism. They have the beneficial effects of anti-inflammation, anti-fibrosis, and angiogenesis on the heart and blood vessels [7]. Since HGF is released after endothelial injury, circulating HGF at a high level is associated with hypertension, diabetes mellitus, smoking, age, body mass index (BMI), and the occurrence and severity of atherosclerotic disease. Despite evidence indicating that HGF is related to the risk factors of ischemic stroke, there are still few studies on the specific correlation between HGF and the disease. Although previous studies have determined that circulating HGF is positively correlated with ischemic stroke and the prognostic factors for stroke development, some limitations exist in the population selection in those studies. Moreover, the correlations of HGF with ischemic stroke and all types of stroke have not yet been determined [8, 9].

Computed tomography perfusion imaging (CTPI) is a novel functional imaging technique that reflects the hemodynamic changes in the living body and performs qualitative, semi-quantitative, and quantitative analyses. It can provide comprehensive imaging and hemodynamic information for clinical purposes in a timely manner, thus guiding clinical treatment. Compared with magnetic resonance imaging (MRI) and perfusion-weighted imaging (PWI), CTPI possesses unique advantages in ultra-early diagnosis of ischemic stroke. This research aims to explore the HGF expression in patients with acute ischemic stroke and its correlations with CTPI and the patients' cognitive functions, hoping to discover new, early diagnosis indicators and prognostic indicators for the disease.

Methods

Clinical case data

Serum samples and the case data from 54 patients with acute ischemic stroke who were hospitalized in the Department of Neurology of our hospital were collected. Inclusion criteria of the research objects: 1) Patients aged over 20, 2) Patients aged 18 to 80, with right handedness, 3) Patients meeting the criteria in the *Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke* and whose acute ischemic stroke was verified via head CT or MRI, and the blood vessels of the head and neck were assessed by virtue of head and neck joint CT angiography (CTA) or digital subtraction arteriography (DSA), 4) Patients with first-onset disease, a stroke attack within 14 days and a National Institute of Health stroke scale (NIHSS) score <15 points, and 5) Patients with normal cognitive function and mental health behavior before the onset, as well as a Hamilton Depression Scale (HAMD) <8 points. Criteria for exclusion: 1) patients diagnosed with ischemic stroke caused by other reasons, such as vasculitis, stroke after surgical operations, and cardiogenic cerebral embolisms, 2) patients with cognitive impairment induced by other diseases, including Parkinson's disease, Parkinsonian syndrome, a medical history of epilepsy and autoimmune diseases in the brain, 3) patients receiving cholinesterase inhibitors and other medicines influencing their cognitive functions during hospitalization, 4) patients with a stenosis degree >50% in blood vessels other than the offending carotid artery and the vertebral artery, as indicated on imaging, 5) patients unable to accomplish cognitive examinations (such as aphasia, apraxia, and visual and auditory impairment) due to a physical functional defect, 6) patients with depression, severe anxiety, drug and alcohol abuse, or a mental disorder, or 7) patients with serious somatic diseases such as cardiac, hepatic and renal dysfunctions.

In addition, blood samples and the related data of 25 healthy people receiving physical examination during the same time period were collected as the control group.

Detection of serum HGF

The enrolled patients were admitted to the Department of Neurology of our hospital for treatment. On the second day after admission, fasting blood was drawn in the morning for routine hematological tests. Serum biochemical examinations were performed by virtue of a Hitachi 7060 fully-automatic biochemistry analyzer. 5 mL fasting venous blood of the patients was collected to determine the serum HGF, which was stored in an ordinary tube for the biochemical examination. After standing at room temperature for 2 h, the blood was centrifuged at 2500 r/min for 15 min. The separated serum was preserved at -70°C for later analysis. An enzyme-linked immunosorbent as-

say (ELISA) was applied to examine the serum HGF, of which the coating of the ELISA plate, the sample test, the color development, and the determination of optical density (OD) were conducted according to the instructions. Moreover, based on the OD value measured, a fitted standard curve and standard equation were obtained, and the HGF level in the samples was calculated in accordance with the standard equation.

Evaluation of cognitive functions

The Mini-Mental State Examination (MMSE) was adapted from the one revised by M. Y. Zhang, which reflects the mental state and cognitive impairment degree of the subjects in a comprehensive, accurate, and rapid manner. The scale was composed of 10 questions, including 30 items in total, measuring and testing their orientation, memory, attention and calculation, language and visuospatial skills. The MMSE scores included seven subitems, namely, 1) orientation (temporal and spatial): 10 points, 2) memory: 3 points, 3) attention and calculation: 5 points, 4) recall: 3 points, 5) language: 5 points, 6) ideomotor application: 3 points, and 7) drawing copying: 1 point. Scoring standards: normal (27-30 points), cognitive impairment (<27 points), mild cognitive impairment (21-26 points), moderate cognitive impairment (10-20 points), and severe cognitive impairment (0-9 points).

Imaging examination

An 128-slice spiral CT machine was utilized for the scanning, and the basal ganglion was selected as the key observation section for the perfusion. 50 mL iodine contrast agent was injected as a bolus from the cubital vein, and a continuous dynamic scan was performed for 5 min in total. After that, the images obtained were transmitted to a workstation and then post-processed using the CT Perfusion (CTP) software package. The region of interest (ROI) was placed in the artery and superior sagittal sinus, respectively, to calculate the perfusion parameters and acquire CTP images, of which all the images were displayed in color. The area of perfusion defect on the CTP was first defined on the diagram of local cerebral blood flow (CBF), with displayed abnormal perfusion areas as the extent of the lesion. Finally, the perfusion parameters such as CBF, local cerebral blood volume (CBV), and mean transit time (MTT) in the lesion areas and corresponding areas on the contralateral side were obtained. The duration of the whole post-processing was 10 min.

Statistical analysis

Statistical Product and Service Solutions (SPSS) 17.0 was adopted for the statistical analysis. The measurement data were presented as the mean ± standard deviation ($\bar{x} \pm s$), and two-sample *t*-tests were used for the intergroup comparisons. The Pearson correlation analysis was adopted for the relevant analyses. $P<0.05$ indicated that the difference was statistically significant.

Results

Comparisons of the patients' general data and total MMSE scores

The general data and total MMSE scores were compared between the patients and the normal control group. There were no statistically significant differences in terms of age or gender among the three groups ($P>0.05$). The difference in the total MMSE score was statistically significant among the three groups ($P<0.01$). As for the pairwise comparisons, the total MMSE score was not statistically different between the anterior circulation stroke group and the posterior circulation stroke group ($P>0.05$). The stroke groups had lower total MMSE scores than the normal control group, with statistically significant differences ($P<0.05$) (**Table 1**).

Serum HGF expressions in each group

The serum HGF levels in the experimental and control groups were measured. The HGF expression levels in the patients with acute ischemic stroke were elevated compared with the normal control group, with a mean difference of up to 1.61 times ($P<0.001$). However, the expression was not significantly different between the anterior circulation stroke group and the posterior circulation stroke group (**Figure 1**; **Table 2**).

Comparisons of the cognitive functions between the groups

Further comparisons of the MMSE subitems between the two groups revealed that there were statistically significant differences in the orientation, attention and calculation, langua-

Table 1. Comparisons of the patients' general data and total MMSE scores

Group	n	Age	Gender (male/female)	MMSE score
Anterior circulation stroke group	24	64.07±1.19	15/9	23.13±1.21
Posterior circulation stroke group	30	63.12±2.18	14/16	24.16±1.32
Control group	25	65.22±1.16	14/11	27.22±2.12*,#
F		0.380	0.921	45.231
p		0.677	0.663	<0.01

Note: *$P<0.05$ vs. the anterior circulation stroke group; #$P<0.05$ vs. the posterior circulation stroke group.

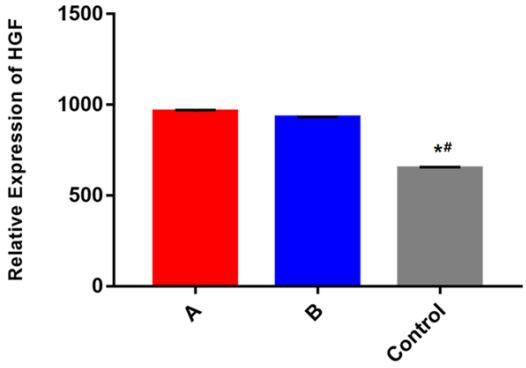

Figure 1. The serum HGF expression levels in each group. The expression level of HGF in patients with acute ischemic stroke was elevated compared with the levels in the normal control group, with a mean difference of up to 1.61 times ($P<0.001$). However, the expression was not significantly different between the anterior circulation stroke group and the posterior circulation stroke group ($P>0.05$). *$P<0.05$ vs. A; #$P<0.05$ vs. B.

ge, ideomotor application, and drawing copying between the stroke group and the normal control group ($P<0.05$), but the differences in memory and recall were not statistically significant ($P>0.05$) (**Table 3**).

Comparisons of the brain CTPI parameters

The CTPI parameters in the patients' penumbra and infarction zones with acute ischemic stroke were compared. The results indicated that the CBF, CBV and positive enhancement (PE) values in the penumbra zone were higher than those in the infarction zone, but the MTT and time to peak (TTP) values in the penumbra zone were lower than those in the infarction zone. All the differences were statistically significant ($P<0.05$) (**Table 4**).

Correlation between the HGF expression and the brain CTPI

The analyses on the correlations between HGF expression and the brain CTPI parameters showed that the HGF expression level was negatively correlated with CBF, CBV, and PE, but it was positively correlated with MTT and TTP ($P<0.05$) (**Table 5**).

Correlation between the cognitive function and the brain CTPI

The correlations between the MMSE scores and the brain CTPI parameters were analyzed. It was shown that the MMSE score was negatively correlated with CBF, CBV, and PE but positively related with MTT and TTP ($P<0.05$) (**Table 6**).

Discussion

HGF, initially described as a mitogen of the liver cells, is an effective angiogenic factor and endothelial specific growth factor influencing a wide range of tissues [10, 11]. Its receptor is transmembrane tyrosine kinase encoded by the proto-oncogene c-Met, which is expressed in multiple types of cells (such as epithelial cells, liver cells, and vascular endothelial cells) [12, 13]. The activation of the receptor in the vascular endothelial cells can lead to cell division, migration and proliferation, the generation and invasion of protease, and neovascularization. Based on those molecular mechanisms, researchers have presumed that HGF plays a role in the natural progression of atherosclerosis, thereby triggering the pathogenesis of cardiovascular diseases, including acute ischemic stroke.

Since HGF has the crucial function of tissue repair in the protection and regeneration of vascular endothelial cells [14], previous studies have also verified that circulating HGF has close associations with such stroke risk factors as hypertension, diabetes mellitus, smoking, age, and BMI [15, 16]. In the research on experimental acute ischemic stroke, the therapeutic method applying HGF so far focuses on the

Table 2. The serum HGF expression levels in each group

Group	n	HGF (ng/mL)	*t*	*p*
Anterior circulation stroke group (A)	24	864.027±91.191	45.231	<0.01
Posterior circulation stroke group (B)	30	894.027±87.191		
Control group	25	665.122±87.163*,#		

Note: *$P<0.05$ vs. the anterior circulation stroke group; #$P<0.05$ vs. the posterior circulation stroke group.

Table 3. Comparisons of the cognitive domain scores under the MMSE scores between the groups

	Stroke group	Control group	*t*	*p*
Orientation/10	7.57±0.87	8.57±0.55	5.270	0.000
Memory/3	2.46±0.91	2.77±0.27	1.665	0.100
Attention and calculation/5	3.27±0.43	4.51±0.81	8.899	0.000
Recall/3	1.96±0.42	2.02±0.36	0.617	0.539
Language/5	3.43±0.19	4.27±0.42	12.290	0.000
Ideomotor application/3	1.97±0.56	2.49±0.64	3.668	0.000
Drawing copying/1	0.59±0.11	0.87±0.21	7.791	0.000

Table 4. Comparisons of the brain CTPI parameters between the penumbra and infarction zones

Group	CBF	CBV	MTT	TTP	PE
Penumbra zone	53.43±21.82	60.43±18.51	129.49±28.41	115.53±13.34	105.93±34.54
Infarction zone	15.43±8.51	25.53±9.70	259.23±68.54	136.46±18.51	43.56±32.86
t	8.393	8.860	11.934	5.714	7.578
p	0.000	0.000	0.000	0.000	0.022

Table 5. Correlation between the HGF expression and the brain CTPI

Group	CBF & HGF	CBV & HGF	MTT & HGF	TTP & HGF	PE & HGF
r	-0.640	-0.521	0.491	0.641	-0.449
p	0.000	0.000	0.001	0.000	0.004

Table 6. Correlation between the MMSE scores and the brain CTPI

Group	CBF & MMSE	CBV & MMSE	MTT & MMSE	TTP & MMSE	PE & MMSE
r	-0.834	-0.789	0.673	0.668	-0.516
p	0.000	0.000	0.000	0.000	0.001

preservation of structure in the stage of acute stroke [17]. Most of those studies are performed on rats, in which the strategy of continuous infusion or genetic transmission is utilized in focal or global cerebral ischemia models [18]. HGF has the effect of promoting regenerated organic factors in physiological activities and can prevent ischemia-induced injuries. However, its functions and mechanism of action under in-vitro pathophysiological conditions still remain to be determined. Some studies have confirmed that the treatment with human recombinant HGF (hrHGF) attenuates the destruction of the blood-brain barrier after persistent cerebral ischemia induced by the embolization of microspheres [19]. Moreover, in the endothelial cells after persistent cerebral ischemia, treatment with hrHGF decreases the expressions of the occludin and zonula occludens-1 (ZO-1) proteins. However, the issue whether the tissue recombination in the stage of subacute stroke is similar to the outcome of long-term functional recovery after treatment discontinuation has not been elaborated in those studies. As a result, the mechanisms related to HGF-induced continuous neurologic

recovery still need to be studied in-depth. In this study, we verified that HGF expression is elevated in patients with acute ischemic stroke, suggesting that HGF plays a certain role in the occurrence and development of the disease. The increase of the HGF level in patients with acute ischemic stroke may be considered one of the compensatory mechanisms for the recovery of neurological function, but further study and analysis are needed.

The evaluation of early ischemic change (EIC) in patients with acute ischemic stroke is of great significance to determining the necessity of treatment with tissue plasminogen activator. In CT examinations, however, there is a lack of consensus on the recognition and quantification of the early changes. Therefore, more experience is needed for the accurate evaluation of EIC. CTA source image (CTA-SI), CTPI, and CTP-CBV can facilitate the EIC evaluation [20]. CTPI, in combination with CT subtraction angiography (CTSA), is able to detect acute ischemic injury in the early and ultra-early stages, as well as distinguish temporary ischemic attack (TIA), lacunar infarction, and the larger infarcted region. With the application of semi-quantitative blood perfusion analysis, CTPI can define the location, area and range of ischemic lesions and penumbras. Those scans can also analyze the status of hemoperfusion in the brain. The early diagnosis of the whole division of the internal or middle carotid artery is very important, and it is meaningful to assess the prognosis and allocation of treatment. In this study, it was proved that the HGF expression level is negatively correlated with cerebral blood flow (CBF), cerebral blood volume (CBV) and positive enhancement (PE), but it is positively correlated with mean transit time (MTT) and time to peak (TTP). It is suggested that the HGF level in patients with acute ischemic stroke is related to CT imaging. The HGF level can reflect patients' cerebral perfusion, which is helpful to understand patients' disease conditions. The possible reason is that the brain tissue injury activates the body's compensatory mechanism and promotes the secretion of HGF, which is related to the patient's condition. However, the research results may be biased due to the small sample size included in this study. Therefore, it is necessary that expand the sample size to obtain more reliable clinical research data.

Disclosure of conflict of interest

None.

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