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Insulin-Like Growth Factor 1 Increases in R-TPA Treated Ischemic Stroke Patients

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Abstract

Background

In Patients and Methods they included 60 patients presenting with acute ischemic stroke; 20 patients were eligible for TPA therapy (group 1 patients) and 40 patients not received r-TPA due to contraindications or came after time window (group 2, control). All patients underwent clinical assessment using NIHSS and quantitative measurement of IGF-1 in serum by ELISA at the onset of stroke (before receiving r-TPA) and at day 7 follow up.

Results

NIHSS was significantly lower and Serum IGF-1 level was significantly higher in day 7compared to that of day 1 in the group (1) patients receiving r-TPA (P-value< 0.001). No significant difference was found in the control group (2). There was a significant negative correlation between age & door to needle time and IGF-1 serum level. There was a significant positive correlation between fo NIHSS and IGF-1 serum level

Conclusion

The r-TPA decrease clinical disability and improve neuroplasticity through increasing serum level of IGF-1.

Keywords: Stroke; r-TPA; Neuroplasticity; NIHSS; IGF-1; insulin-like growth factor.

Introduction

Cerebrovascular diseases are the second leading cause of death and the leading cause of disability (1) Annually, 15 million people suffer stroke worldwide; of these, 5 million dies and another 5 million are left permanently disabled (2) intravenous (IV) recombinant tissue plasminogen activator (r-TPA) was approved for use 1996, and become the main therapy for acute stroke treatment across the world (3)Some findings suggest that intravenous therapy with r-TPA might have neuroprotective properties in addition to its thrombolytic action (4) IGF-1 is the mediator of the anabolic and mitogenic activity of growth hormone(5) and promote cell survival and division in CNS (6)Lower IGF-1 levels are significantly related to the risk of ischemic stroke occurrence (7). This study aimed to determine the effect of treating patients with acute ischemic stroke with r-TPA on disability as measured by NIHSS and serum Insulin-Like Growth Factor 1 (IGF 1) level as a marker of neuroplasticity and to correlate clinical results to IGF 1 level.

Patients and methods

Patients

The current study is a prospective case-control study, conducted on Sixty consecutive patients with acute ischemic stroke (AIS).

Patients were defined according to the World Health Organization (WHO) criteria were recruited from stroke care units of Fayoum university hospitals during the period from March (2019) to January (2020).

The patient's disability assessed according to National Institutes of Health Stroke Score NIHSS with the score ranging from 0 to 42. Scoring and Outcomes; 0= no stroke 1-4= minor stroke 5-15= moderate stroke 15-20= moderate/severe stroke 21-42= severe stroke (8); men and women with AIS; age <80 years old were included, They were divided into two groups:

Group 1: Patients with the diagnosis of acute ischemic stroke (AIS) in the therapeutic window (first 4.5 hours) and have no contraindications for r-TPA treatment, They were treated with intravenous (IV) r-TPA (0.9 mg/kg). They were twenty patients

Group 2: patients with a diagnosis of AIS in the therapeutic window but have contraindications for r-TPA or came after 4.5 hours from the onset of stroke. They were forty patients. They considered as the control group.

Ethical consideration

The study was approved by the faculty of medicine Fayoum university ethical committee and carried out in compliance with the Helsinki Declaration. Written informed consents were obtained from all patients and control.

Methods

All patients were subjected to the followings: Detailed history taking with particular emphasis on demographic data, and vascular risk factors, Thorough general and neurological examination were done.

Brain CT: to assess the size of the ischemic infarction and exclude any structural lesion or hemorrhage and(Toshiba Scanner
Activion, Model TSX-031A 3D Volume, Japan).

Patients were followed up for one week from the first event. Stroke disability was reassessed by NIHSS. IGF level was also measured.

Sample preparation

venous blood samples were taken from all patients (group I)on admission before receiving r-TPA and a second sample was taken seven days after stroke onset and receiving r-TPA as a treatment. For the control group (group II), blood samples were taken at admission and seven days after stroke onset. Samples kept 15 minutes for clotting then centrifuged for 20 minutes at 2,000-3,000 rpm. serum was separated and kept under -80 c.

ELISA procedure

Before use, the kit and sample warmed naturally to room temperature Assay procedure. We add 50µl standard to standard well, and 40µl sample to sample wells and then add 10µl anti-IGF-1 antibody to sample wells, all wells are pre-coated with IGF-1 monoclonal antibody, we add 50µl streptavidin-HRP to all wells (sample and standard wells). we mix well and cover the plate and incubate it for 60 minutes at 37°C.

Then we wash the plate 5 times with wash buffer, We add 50µl substrate solution A to each well and then add 50µl substrate solution B to each well, and incubated for 10 minutes at 37°C in the dark. Add 50µl Stop Solution to each well, Determine the optical density (OD value) of each well immediately within 30 min after adding the stop solution at 450 nm

Statistical analysis

The sample size was calculated according to Epi Info2000, a special formula used based on the prevalence of disease at a confidence interval of 95% and a precision of 2%. The sample increased by 10% to overcome problems related to missing data

Data were collected, coded, and analyzed using Statistical Package for Social Science (SPSS version 16 . Chicago IL, USA). comparison between two study groups was done using a student t-test for quantitative variables. A chi-square test was used to compare qualitative variables. Peason correlation co-efficient used to test the association between quantitative normally distributed variables. P-value <0.05 used as the cut off value for statistical significance.

Results

The study groups(patients received r-TPA group I and the control group 2) are well-matched as regarded age(p=0.273) ,sex(p=0.348), risk factor(hypertension (p=0.715),DM(p=0.846 and smoking(p=0.566) grade of disability NIHSS(p= 0.832)and ILGF1 serum level on admission(p=0.929) table (1)NIHSS significantly decrease in the 7th day in the patients of group I patients received r -TPA denoting significant clinical improvement; in comparison to their initial score on admission table and in comparison to the NIHSS of the control group table (2).

While NIHSS did not differ in the control group on the7th days after stroke in comparison to their initial NIHSS on admission.

IGFI serum level at the1st day of the stroke, in patients of groups (group I before receiving r-TPA and control group), was nearly the same table (2)at the 7th day of stroke IGF1 serum level significantly increased in group I; patients received r-TPA (from 143.6±76.2 to160.9±75.7,P <0.001*)

denoting plasticity while the control group no significant difference noticedThere was a significant negative correlation between age of patient and IGF-1 serum level measured at the onset of stroke before receiving r TPA (r coef.=-0.848, P-value <0.001) and at 7th day of stoke after receiving r TPA (r coef.=-0.826, P-value<0.001) figure (1) and(2) There was a significant negative correlation between the door to needle time and IGF-1 serum level measured in cases after 7 days from r-TPA injection (r coef.=-0.505, P-value=0.023)There was significant positive correlation between NIHSS and IGF-1after 7 days from the r-TPA injection (r coef.=-0.714, P-value=0.0001)

Figure 1: Correlation between age and IGF-1 levels at baseline in patients of group 1.

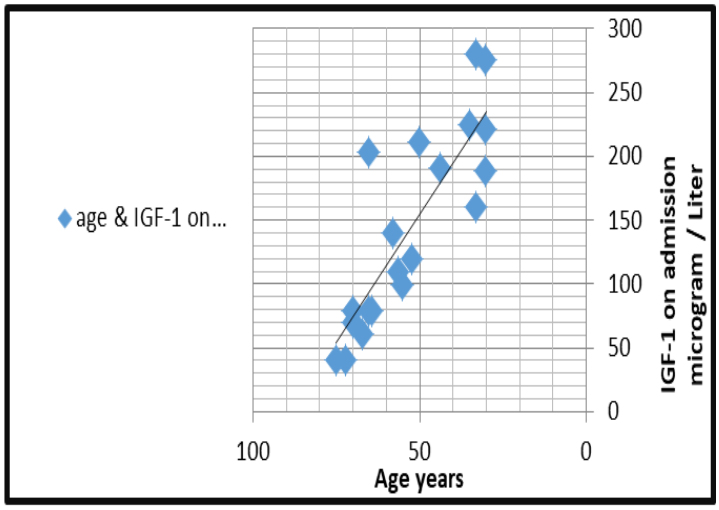

Figure 2: Correlation between age and IGF-1 levels after 7 days follow up in patients of group 1.

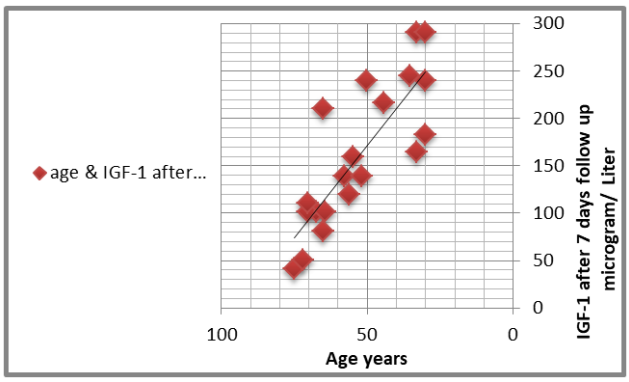

Table 1: Comparison of demographic data, risk factors of stroke, clinical assessment of disability (NIHSS) and serum level of marker insulin-like growth factor 1 between study groups.

Demographic data		Group I (n=20)	Group II (n=40)	P-value
		N (%)	N (%)	
Age	<60 years	12(60%)	18(45%)	0.273
	≥60 years	8(40%)	22(55%)	
	(mean±SD)	52.7±16.04	59.15±13.9	
Gender	Male	14(70%)	23(57.%)	0.348
	Female	6(30%)	17(42.5%)	
Risk factors of stroke				
Hypertensive		11(55%)	20(50%)	0.715
Non-hypertensive		9(45%)	20(50%)	
Diabetic		7(35%)	13(32.5%)	0.846
Non diabetic		13(65%)	27(67.5%)	
Atrial fibrillation		6(30%)	7(17.5%)	0.268
No atrial fibrillation		14(70%)	33(82.5%)	
Smoker		8(40%)	13(32.5%)	0.566
Non-smoker		12(60%)	27(67.5%)	
NIHSS		11.1±3.35	11.3±4.1	0.832
IGF1 serum level		143.6±76.2	142.1±54.4	0.929

Table 2: Comparison between clinical and laboratory assessment of patients groups at 1st day and 7th day of stroke.

Clinical and laboratory assessment	Group I (n=20) (Mean±SD)	Group II (n=40) (Mean±SD)	P-value
NIHSS in 1st day of stroke	11.05±3.35	11.3±4.1	0.832
NIHSS in 7th day of stroke	7.1±5.24	10.8±4.4	0.006*
IGF1 in 1st day of stroke (microgram/L)	143.6±76.2	142.1±54.4	0.929
IGF1 in 7th day of stroke (microgram/L)	160.9±75.6	145.6±54	0.369

Discussion

In this study, there was a significant improvement in NIHSS on the 7th day of r-TPA infusion in patients of group 1. Whereas control group patients did not have significant improvement. Similarly, previous studies reported a significant decrease in NIHSS during follow up patients with stroke treated with r-TPA (9,10) Several studies indicated that r-TPA has beneficial effects that are independent of its thrombolytic action consistent with functional recovery of stroke patients after r-TPA treatment, attribute it to neuroplasticity (4)

In the present study, significantly higher IGF-1 serum level at 7th day in patients received r-TPA compared to their baseline IGF-1 serum level. Whereas the control group did not show a significant increase. Similarly, a previous study found that higher serum levels of IGF-I at the time of stroke are significantly correlated with a better outcome in 1 year of follow-up IGF-I influences neuronal growth, excitability, and release of the neurotransmitters. It is an endogenous factor for neurons, glial and endothelial cells survival, enhance functional recovery after injury by stimulating the precursors of neural and oligodendrocyte to proliferate.

In this study, there was a negative significant correlation between age and IGF-1 serum level measured at the stroke onset and at follow up, so the age of the patient affects the serum level f IGF 1 and neuroplasticity. Similar to our findings reported that serum IGF-I levels decreased with age. Aging negatively affects the cellular proliferation and the survival of immature neurons and this leads to decrease CNS neurogenesis.

Early thrombolytic therapy in acute ischemic stroke has proven to reduce the associated morbidity.In the present study, there was a negative significant correlation between the door to needle time and IGF-1 serum level in group1 patients. so shorting the door to needle time was associated with an increased level of IGF 1 denoting better neuroplastic response. This was in agreement with who found that decrease DTN is associated with improving patient outcomes. AS with time lost is brain lost, 2 million nerve cells are lost each minute in which reperfusion has not been achieved. Also, others provide convincing evidence of a time-dependent benefit of thrombolytic therapy. Every 10 minutes in which therapy is delayed, one fewer of each hundred treated patients benefits.

In the present study, in agreement with (19,20,11 and 21), there was a significant positive correlation between NIHSS and IGF-1 serum levels. adding evidence that IGF-1 may exert a neuroprotective effect.There are some limitations in this study: IGF binding protein (IGFBP) was not measured in this study, such binding protein may affect the serum level of IGF. This study follows up a measurement of IGF-1 after only one week

Conclusion

The r-TPA improves clinical outcomes and improves neuroplasticity via increasing serum level of IGF-1. There is significant correlation between age, door to needle time & insulin like growth factor

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