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EVALUATION OF SERUM FIBROBLAST GROWTH FACTOR LEVELS IN ACUTE ISCHEMIC STROKE

AKUT İSKEMIK İNMEDE SERUM FIBROBLAST BÜYÜME FAKTÖRÜ DÜZEYLERININ DEĞERLENDIRILMESI

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ABSTRACT

Introduction: Stroke is a leading cause of death worldwide and remains very difficult to treat. Stroke results in brain damage through a cascade of events, including inflammatory responses and apoptosis. Serum basic fibroblast growth factor (bFGF) promotes the survival of nerve cells, stimulates new vessel formation, mesodermal remodeling, cell division, and cell migration, and accelerates wound healing. In this study, we evaluated serum bFGF levels in patients with ischemic stroke and examined the relationship between the clinical status of ischemic stroke patients and the control group.

Methods: We prospectively evaluated 96 patients (38 female and 58 male) admitted to our Neurology Clinic between February 2012 and October 2012, whose diagnosis of ischemic stroke was confirmed within 24 h after the onset of ischemic stroke. The control group comprised 48 age- and sex-matched healthy volunteers (32 female and 16 male) without vascular risk factors. the initial neurologic evaluation was performed using the National Institutes of Health Stroke Scale (NIHSS) to determine the severity of the stroke, and blood samples were obtained from all patients included in the study within 24 h from the onset of stroke to measure serum bFGF levels. These data were compared with data from control subjects.

Results: Serum bFGF levels of the ischemic stroke patients and the control group were 6.6±8.8 pg/ml and 4.6±4.3 pg/ml, respectively. A significant difference was noted between serum bFGF levels of both ischemic stroke patients and control subjects (p=0.005). Serum bFGF levels did not correlate significantly with NIHSS scores of patients with ischemic stroke (p>0.05).

Conclusions: We found that serum bFGF levels were significantly increased after acute ischemic stroke. The increase in serum bFGF levels in ischemic stroke patients may be a protective response to reduce brain damage.

Keywords: Basic fibroblast growth factor, Intracerebral ischemia, Angiogenesis, Acute ischemic stroke

ÖZET

Giriş: İnme, dünya çapında önde gelen bir ölüm nedenidir ve tedavisi hala çok zordur. İnme, inflamatuar yanıtlar ve apoptozis de dahil olmak üzere bir dizi olay yoluyla beyin hasarına neden olur. Serum bazik fibroblast büyüme faktörü (bFGF), sinir hücrelerinin hayatta kalmasını destekler, yeni damar oluşumunu, mezodermal yeniden şekillenmeyi, hücre bölünmesini ve hücre göçünü uyarır ve yara iyileşmesini hızlandırır. Bu çalışmada, iskemik inmeli hastalarda serum bFGF düzeylerini değerlendirdik ve iskemik inmeli hastaların klinik durumu ile kontrol grubu arasındaki ilişkiyi inceledik.

Yöntemler: Şubat 2012 ile Ekim 2012 arasında Nöroloji Kliniğimize başvuran ve iskemik inme tanısı iskemik inmenin başlangıcından sonraki 24 saat içinde doğrulanan 96 hastayı (38 kadın ve 58 erkek) prospektif olarak değerlendirdik. Kontrol grubu, vasküler risk faktörleri olmayan 48 yaş ve cinsiyete eşleştirilmiş sağlıklı gönüllüden (32 kadın ve 16 erkek) oluşuyordu. İlk nörolojik değerlendirme, felcin şiddetini belirlemek için Ulusal Sağlık Enstitüleri İnme Ölçeği (NIHSS) kullanılarak yapıldı ve çalışmaya dahil edilen tüm hastalardan, serum bFGF seviyelerini ölçmek için inmenin başlangıcından itibaren 24 saat içinde kan örnekleri alındı. Bu veriler, kontrol deneklerinden alınan verilerle karşılaştırıldı.

Bulgular: İskemik inme hastalarının ve kontrol grubunun serum bFGF seviyeleri sırasıyla 6,6±8,8 pg/ml ve 4,6±4,3 pg/ml idi. Hem iskemik inme hastalarının hem de kontrol deneklerinin serum bFGF seviyeleri arasında anlamlı bir fark kaydedildi (p=0,005). Serum bFGF seviyeleri, iskemik inme hastalarının NIHSS puanlarıyla anlamlı bir şekilde ilişkili değildi (p>0,05).

Sonuç: Akut iskemik inmeden sonra serum bFGF seviyelerinin anlamlı şekilde arttığını bulduk. İskemik inme hastalarında serum bFGF düzeylerindeki artış beyin hasarını azaltmak için koruyucu bir yanıt olabilir.

Anahtar Kelimeler: Temel fibroblast büyüme faktörü, İntraserebral iskemi, Anjiyogenez, Akut iskemik inme

INTRODUCTION

Ischemic stroke is defined as an acute cerebrovascular disease resulting from the occlusion of blood vessels that prevent blood flow to the brain (1). Stroke is a major cause of death worldwide. The incidence of ischemic stroke is increasing in developing countries and is among the leading causes of disability (2). In addition, the number of individuals

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experiencing the paralytic effects of stroke is increasing day by day (3).

Neurorestorative progression in stroke is characterized by angiogenesis, neurogenesis, and synaptic plasticity, which are beneficial for functional recovery (4). Newly formed blood vessels speed up cerebral blood flow in the ischemic area by supplying oxygen and nutrients to the ischemic area and improve neurological function (5). Therefore, promoting angiogenesis is a promising therapeutic strategy for the treatment of ischemic stroke. New-generation biochemical markers such as serum bFGF levels may be helpful in the diagnosis of ischemic stroke patients, stroke type and mortality rates.

Fibroblast growth factors (FGFs) are polypeptide growth factors involved in numerous processes, including cell growth, development, neuronal function, metabolism, proliferation, migration, apoptosis, wound repair, and angiogenesis (6). FGFs support blood vessels to help deliver nutrients to the brain and other organs (7). Thanks to their homeostatic functions, they promote tissue repair and accelerate wound healing (8). The angiogenic and neurotrophic properties of FGFs suggest that they may be effective in the treatment of ischemic stroke. FGFs also contribute to neuroprotection, neuroregeneration, vascular protection, angiogenesis, and blood-brain barrier protection after ischemic stroke. As such, FGFs may be candidate agents that act via multiple pathways to improve the outcomes of stroke patients. Thus, bFGF will provide new information on the recovery of ischemic stroke and will be helpful in treatments.

The aim of this study was to determine the serum levels of basic fibroblast growth factor (bFGF) in patients with ischemic stroke and the control group and to determine the role of bFGF in stroke diagnosis through its correlation with National Institute of Health Stroke Scale (NIHSS) scores in patients with ischemic stroke.

METHODS

The prospective study was conducted in the Department of Neurology between February 2012 and October 2012 on 96 patients (38 female and 58 male) who were hospitalized following diagnosis of ischemic stroke, which was confirmed by neuroradiological examination performed within 24 h after the event. These patients received treatment following detailed anamnesis, as well as physical and neurological examinations.

Ethics approval was obtained from the Local Ethics Committee before initiating the study (decision no: 2011/223; dated 01.12. 12).

Those with a history of systemic diseases, including chronic neurologic disease, head trauma, uremia, liver cirrhosis, cancer, and chronic lung and liver diseases, were excluded.

Our group consisted of 48 age-matched healthy volunteers (32 women and 16 men) who were relatives of patients who applied to the neurology outpatient clinic and did not have any vascular risk factors. Detailed history of vascular risk factors, medications used, neurologic examination results, NIHSS scores, and blood pressure data were recorded at the Department of Neurology.

For the initial neurologic evaluation, the level of consciousness, conscious response to questions, responsiveness to commands, extraocular movements, visual fields, facial paralysis, arm and leg motor movements, limb ataxia, sensation, aphasia, dysarthria, and degree of neglect were assessed using the NIHSS score. For the measurement of bFGF levels, 10 ml of blood was drawn from the antecubital vein of patients within 24 h after the onset of stroke and from all healthy volunteers. Blood samples collected in gel tubes used for biochemical testing were left to clot for 20-30 minutes and then centrifuged at 8000-10000 rpm for 10 minutes. Serum was separated and placed in individually labeled Eppendorf tubes and stored at -50°C until the day of analysis. On the day of analysis, frozen serum samples were allowed to thaw at room temperature. Serum bFGF levels were measured using an enzyme-linked immunosorbent assay kit (Human bFGF, Ray Biotech, GA, USA, P09038). Additionally, blood tests were performed to measure possible significant differences in hs-CRP and hemogram values between the patient and normal control groups.

Statistical analysis

SPSS (Statistical Package for Social Sciences) 11.5 PC (SPSS Inc., "SPSS 11.5 for Windows," Chicago, IL, USA, 2002.) program was used for all statistical analyses. The conformity of the data to normal distribution was assessed using the Kolmogorov-Simirnov test. For descriptive statistics, number, percentage, mean ± standard deviation (ss), median, minimum (min), and maximum (max) values were used. Since the data did not conform to normal distribution, Mann Whitney U, Kruskal Wallis tests and Spearman correlation analysis were used in comparisons between groups. The chi-square test (and/or Fisher's exact test) was used to analyze categorical variables. A p-value of <0.05 was accepted to indicate statistical significance.

RESULTS

The study included a total of 96 ischemic stroke patients (58 [78.4%] males and 38 [54.3%] females) and 48 controls (16 [21.6%] males and 32 [45.7%] females). Distribution of stroke status of the study group according to sociodemographic characteristics (Table 1). Descriptive characteristics of the patient and control groups are presented in Table 2.

The mean bFGF levels of the 15 patients who died due to stroke and the 81 patients who survived were 5.9±5.4 pg/ml

Table 1. Distribution of stroke status of the study group according to sociodemographic characteristics

Sociodemographic Characteristics	Stroke			Test Value x^2;p
	Yes (Patient) n(%)[a]	None (Normal Control) n(%)[a]	Total n(%)[b]	
Age Group				
Under 65	20(57.1)	15(42.9)	35(24.3)	1.887; 0.187
65 and over	76(69.7)	33(30.3)	109(75.7)	
Gender				
Male	58(78.4)	16(21.6)	74(51.4)	9.396; 0.002
Female	38(54.3)	32(45.7)	70(48.6)	
Total	96(66.6)	48(33.3)	144(100.0)	

a: Row percentage
b: Column percentage
Note: This table displays descriptive statistics for each data. The estimated statistics are n(%) and/or mean, minimum, maximum and standard deviation (SD)

and 6.6±8.8 pg/ml, respectively (p=0.361).The white blood cell count (WBC) differed significantly between the ischemic patients and control groups (p<0.0001). There was no significant difference between the groups in terms of platelet count (p=0.497), hematocrit (p=0.309), and hemoglobin level (p=0.12). LDL levels were significantly higher in normal controls. There was no correlation between serum bFGF level and NIHSS score in patients with ischemic stroke (p>0.05), whereas a moderately positive correlation existed between NIHSS score and Hs-CRP (High-sensitive C-reactive protein) level (r=0.413; p=0.011).

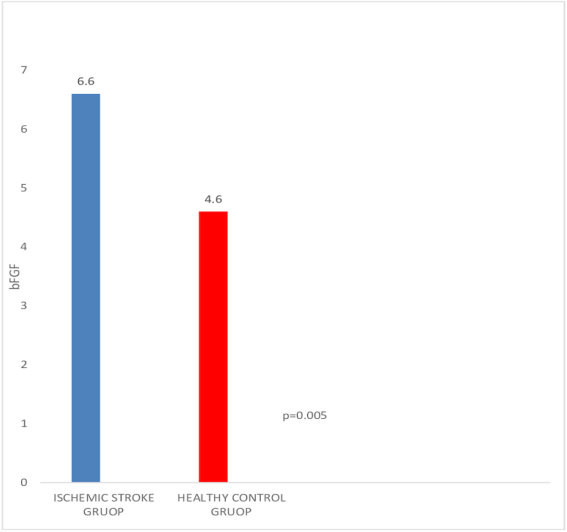

Figure 1. bFGF levels between ischemic stroke and healthy control groups

As shown in Figure 1, bFGF levels differed significantly between the ischemic stroke and healthy control groups (p=0.005).

Table 2. Distribution of stroke status of the study group according to related variables

Related Variables	Patient (Median) Q1-Q3	Control (Median) Q1-Q3	Test Value	
			u	p
WBC (1000x)	7.9(6.4-9.8)	6.4 (5.2-7.8)	1.353	<0.001*
Hct (%)	39.9 (36.3-43.0)	41.1 (38.8-43.2)	2.554	0.289
Hs-CRP (mg/dl)	16.2 (10.3-28.5)	6.9 (4.2-8.9)	6.881	<0.001*
Hb	13.2 (11.8-14.2)	13.7 (12.9-14.3)	2.748	0.060
MCV	88.2 (84.0-92.0)	89.0 (87.0-92.0)	2.576	0.248
bFGF (pg/ml)	349.2 (56.7-1029.4)	255.4 (0.0-782.3)	1.991	0.214
NIHSS scores	5.0(2.0-11.5)	0.0 (0.0-0.0)	9.966	<0.001*
LDL	106.0 (88.4-130.8)	125.8 (105.2-152.8)	2.631	<0.001*

Note: This table displays descriptive statistics for each data. The estimated statistics are mean, minimum, maximum and standard deviation (SD)
Abbreviations:WBC: White blood cell count; Hct:Hematocrit; Hs-CRP:High-sensitive C-reactive protein; MCV: Mean corpuscular volume; Hb: Hemoglobin; bFGF: Basic fibroblast growth factor;
NIHSS; National Institutes of Health Stroke Scale ; LDL, Low-density lipoprotein

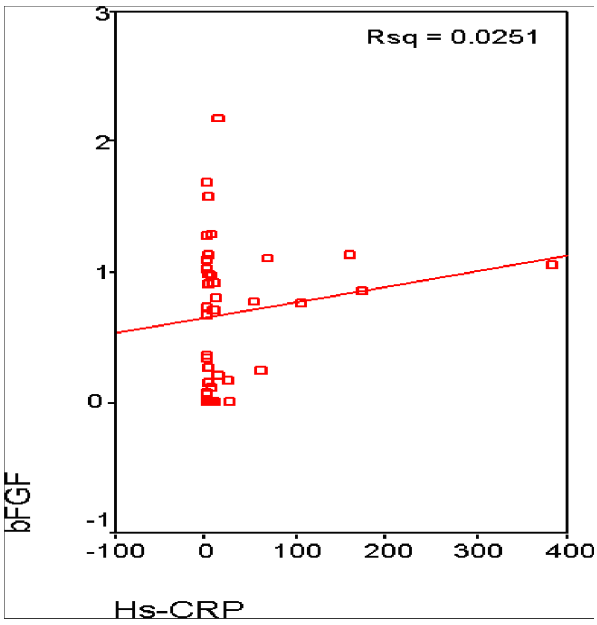

Figure 2. Correlation between Hs-Crp and bFGF values

As seen in Figure 2, any statistically significant correlation was found between Hs-Crp and bFGF values (p= 0.694).

DISCUSSION

Polypeptide growth factors are important for molecular and cellular processes involved in functional recovery and wound healing after an episode of acute stroke. Brain injury triggers the release of different growth hormones to protect the brain from excitotoxicity, hypoxia, acidosis, and oxidative stressThe main source of the growth hormone bFGF in the brain is glial cells, although it is also expressed by other types of neurons. Together with other fFGFs, bFGF plays an important role in many different processes, such as nerve regeneration, chronic inflammation, and wound healing. bFGF is a potent angiogenic factor that promotes the migration and proliferation of endothelial cells and also plays a role in other metabolic processes (9). Angiogenesis, which is associated with survival, is accelerated in the brain tissue of stroke patients. Increased bFGF levels were found mostly in the ischemic penumbra region of stroke patients to have contributed to increased angiogenesis and blood flow (10). bFGF protects neurons against toxic insults and ischemic neuronal disorders (11). After experimentally induced stroke mouse model, bFGF treatment was found to promote neurogenesis, reduce infarct volume and accelerate functional recovery. bFGF levels increase after cerebral ischemia, which may be related to increased vascularization. A study by Lanfrankomi et al. (12) supported the neuroprotective role and neurogenesis effects of bFGF. However, a phase II/III trial conducted in North America was stopped after review of data from 300 patients with acute ischemic stroke due to higher mortality rates in the bFGF-treated group compared to the control group (13). A European-Australian phase II/III randomized study in 286 acute ischemic stroke patients confirmed that 5 or 10 mg trafermin (recombinant human bFGF: rhbFGF) or placebo infused intravenously for 24 h did not provide any significant neuroprotection versus intravenous administration, but instead caused dose-dependent damage. Moreover, hypotension and increased mortality rates were noted among treated patients (14).

Guo H et al. conducted a study in China and found a significant increase in serum bFGF levels in 30 acute ischemic stroke patients compared to the control group (15). Relatively higher serum bFGF levels were also observed in our study. Angiogenesis is important to help the neuronal tissue recover from neurological deficits after cerebral ischemia and ensure neuronal survival. bFGF is a potent stimulator of angiogenesis occurring after cerebral ischemia. FGFs can be used in the treatment of stroke due to their pharmacological effects on multiple targets, including the ability to directly promote neuronal survival, increase angiogenesis, protect against blood-brain barrier disruption, regulate microglia, reduce infarct size, and improve neurological function (16). In a study examining the roles and therapeutic potential of fibroblast growth factors in the treatment of ischemic stroke demonstrated the protective effects of bFGFs in a stroke model (17).

Serum FGF levels in patients with acute ischemic stroke were found to be significantly higher than those in the control group (18). In healthy individuals, very low or even undetectable levels of bFGF were recorded, whereas increased levels of bFGF were found in the serum of patients with diabetes and coronary artery disease (19). In a previous study, bFGF levels were found to be significantly higher in the serum of 16 patients with intracerebral hemorrhage and 28 patients with ischemic stroke compared to healthy controls (20). In our study, we similarly found increased bFGF levels in the serum of patients with ischemic stroke. It is known that hs-CRP levels are high in patients with stroke (21). Similarly, in our study, Hs-CRP levels were found to be higher in the case group than in the control group. Increased serum bFGF levels may be a protective response to prevent secondary damage after acute ischemia in patients with ischemic stroke. Unlike the previous study, the relationship of bFGF levels with clinical findings was also investigated in our study. The bFGF levels was not found to be associated with NIHSS scores. These findings showed that levels of bFGF increase after ischemic stroke, and serum bFGF levels may provide valuable information for predicting infarct size and clinical prognosis after ischemic stroke.

In our study, the sample size was not large enough, with 96 patients and 48 controls. Since findings on changes in bFGF levels over time in patients with acute cerebral infarction were not reported, more evidence would support stronger results.

In this study, serum bFGF levels are high in the initial phase of acute cerebral infarction. Further studies are needed to determine the changes in bFGF levels in serum after days of cerebral infarction.

CONCLUSION

In conclusion, this study showed that serum bFGF levels significantly increase after acute ischemic stroke. The increase in bFGF levels in these patients may be a protective response to reduce brain damage or may be related to angiogenesis. Due to an urgent need for the development of new and more effective medications, future research on bFGFs should be conducted to achieve better treatment outcomes with bFGFs among ischemic stroke patients. Continued research on the utility of bFGF as a novel drug candidate in the treatment of cerebral ischemia will provide new insights into the involvement of bFGF in neuronal recovery after ischemic stroke.

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Ethics Committee Approval: Ethics approval was obtained from the Düzce University Ethics Committee before initiating the study (decision no: 2011/223; dated 01.12. 12).

Informed Consent: An informed consent form was obtained from the patient/patient's representative to collect and publish the patient's clinical information.

Authorship Contributions: Idea/Concept:ŞŞ, MŞ, SD, HA, HD, Design: ŞŞ, MŞ, SD, HA, HD, Supervision: ŞŞ, MŞ, SD, HA, HD, Data Collection and Processing: ŞŞ, MŞ, SD, HA, HD, Analysis or Interpretation: ŞŞ, MŞ, SD, HA, HD, Literature Search:ŞŞ, MŞ, SD, Writing: ŞŞ, MŞ, SD, Critical Review: ŞŞ, MŞ, SD, References and Fundings: -, Materials: ŞŞ, MŞ, SD.

Conflict of Interest: None.

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