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Experimental Medicine

The Study of the VEGF and TGF among Patients with Ischemic Stroke

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(Presented by Academy Member Ramaz Khetsuriani)

Abstract. Ischemic stroke (IS) is one of the most common causes of disability and mortality worldwide. The development of ischemic stroke is associated with many factors. It is noteworthy that growth factors, including VEGF and TGF, have a significant impact on ischemic stroke. Both play an essential role in regulating many processes in normal tissue. The present work examines the role of VEGF and TGF in patients with ischemic stroke. The ELISA method was used to study the levels of TGF and VEGF. A total of 24 samples were studied. Specifically, 12 were in the control group (healthy), and 12 patients had ischemic stroke. Statistical analysis of the experimental data (descriptive statistics and t-test) was performed using GraphPad Prism version 10. Statistical significance was considered $p < 0.05$. The study showed that VEGF levels were increased ~1.5-fold in patients with ischemic stroke compared to controls ($p = 0.0474$); statistical significance was considered at $p < 0.05$. The study showed that VEGF levels were increased ~1.5-fold in patients with ischemic stroke compared to controls ($p = 0.0474$). We believe that VEGF and TGF may be associated with critical vital indicators of the post-stroke recovery process. We believe it is vital to expand our research, which may provide additional information on essential aspects related to the development of therapeutic strategies for stroke management. Thus, VEGF and TGF may play a crucial role in post-stroke recovery processes, which highlights their potential use as both therapeutic and prognostic biomarkers in guiding the treatment of ischemic stroke.

Keywords: VEGF, TGF, ischemia, stroke

Introduction

Ischemic stroke (IS) is one of the most disabling and fatal diseases around the world (Gorelick, 2019) (Li et al., 2024). Development of IS is connected to several factors (Babkina et al., 2022) (Boehme et al., 2017) (Nakashidze et al., 2021) (Nakashidze et al., 2022) (Liu et al., 2024). TGF (transcription growth factor) is a group of proteins that are predominantly produced by T lymphocytes (Chin et al., 2004) (Liu et al., 2024) and are responsible for regulating various cellular processes, including cell growth/differentiation/extracellular matrix production/immune responses (Naka & Hirao, 2017) (Deng et al., 2024). Divided into alpha, beta, and gamma types, they all play a critical role in the extensive functions and mechanisms of action, including, but not limited to, tissue

repair, homeostasis, and the pathogenesis of diseases such as cancer, fibrosis, and autoimmune disorders. It is well known that TGF-Beta has regulatory functions on a wide variety of cell types, also including the following biological processes: regulating hematopoiesis/cell replication/differentiation, cell-cycle progression/angiogenesis, etc. (Zhang & Yang, 2020). These processes are imperative to the physiological functioning of the human body, and therefore, functioning and levels of TGF (beta) can provide helpful insight into diseases and pathological events. Considering its role in angiogenesis, it may serve as a valuable marker for evaluating the repair mechanisms after ischemic stroke. Another signalling molecule, known as VEGF (vascular endothelial growth factor or VPF, also referred to as vascular permeability factor), is produced by various cell types, including macrophages, platelets, renal mesangial cells, and even tumour cells. It plays a vital role in disease-related angiogenesis and the development of lymphatic vessels (Holmes & Zachary, 2005). In adults, angiogenesis is also essential during pregnancy and in tissue growth and repair, playing a crucial role in the pathogenesis of various human diseases, including cancer. Therefore, it is logical that an ischemic event, such as a stroke, may exhibit increased serum levels of VEGF as it participates in the tissue repair mechanisms that was damaged during the pathological event. VEGF-A is also the most important regulator of blood vessel formation (Holmes & Zachary, 2005). It is now well established that VEGF plays an imperative role in the cardiovascular system, and research from the early 2000s supports the fact that the co-expression of VEGF and its receptors on myofibroblasts (Chintalgattu, 2003) would suggest its role in tissue remodelling at the site of infarction using autocrine pathway(s). Classical literature establishes the uptake of oxidised LDL by macrophages as the initiating step in the formation of so-called “foam cells” in atherosclerotic lesions (Ross, 1993). The studies mentioned here are only part of the significant research that has led to a reluctant admission of the role of VEGF in atherosclerosis (Yang et. al. 2003). Specifically, VEGF is capable of increasing vessel permeability to LDL, forming a dangerous slope for an atherosclerotic event and/or aggravating an ongoing one. According to the investigation, TGF and VEGF may have significant utility in determining the impact of ischemic strokes on patients by aiding in prognostication and providing a cost-effective method for identifying patients at higher risk, with the help of other biomarkers. Furthermore, as an extension, it may help determine the disability a stroke event may cause (Hong et al., 2025).

Ischemic stroke is regarded as a condition with high morbidity and mortality. We aimed to study the levels of TGF and VEGF in patients with ischemic stroke compared to a control group, investigating a potential link with the ischemia.

Materials and Methods

We used the enzyme-linked immunosorbent assay (ELISA) methods for the investigation of TGF and VEGF levels. A total of 24 samples were studied – specifically, 12 in the control group (healthy) and 12 patients with ischemic stroke. Statistical analysis of experimental data (descriptive statistics, t-test) was performed using GraphPad Prism version 10; $p < 0.05$ was considered statistically significant.

Results and Discussion

The study revealed that levels of TGF and VEGF were increased in Ischemic stroke compared to the control group. VEGF levels were ~1.5-fold higher ($p = 0.047$), and TGF levels were ~1.8-fold higher ($p = 0.001$) (Table; Fig. A, B)

Table. The study of the VEGF and TGF in schemic Stroke

Study population	VEGF, pg/ml Mean± SEM	TGF- pg/ml Mean± SEM
Control group	28.67 ± 5.433	6.707 ± 0.9234
IS	42.33 ± 3.419	12.20 ± 1.681
P value	0.0110	0.0474

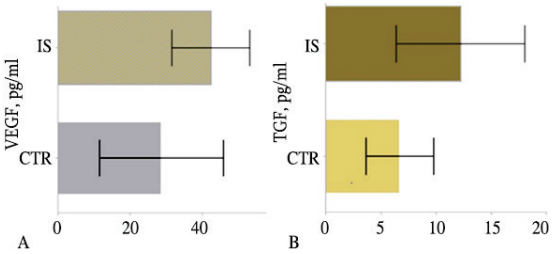

Fig. The study of the VEGF (A) and TGF (B) in ischemic stroke.

The findings of this study robustly indicate that the levels of both VEGF and TGF are increased in patients who experienced an ischemic stroke compared to healthy control individuals. Specifically, our analysis revealed that VEGF levels were significantly elevated ($p = 0.0474$) in the stroke patient group (42.33 ± 3.419 pg/ml, $n = 12$) compared to the control group (28.67 ± 5.433 pg/ml, $n = 12$), representing an approximate 1.5-fold increase. Similarly, we observed a statistically significant increase in TGF levels ($p = 0.0110$) in the ischemic stroke group (12.20 ± 1.681 pg/ml, $n = 12$) compared to the control group (6.707 ± 0.9234 pg/ml, $n = 12$), indicating an approximate 1.8-fold increase based on the means.

Our finding of significantly elevated VEGF in patients with ischemic stroke strongly aligns with a substantial body of pre-existing scientific literature. VEGF, a key regulator of angiogenesis and vascular permeability, is known to be upregulated in response to tissue injury, including that caused by ischemic events. The observed increase in our study (approximately 1.5-fold, $p = 0.0474$) is consistent with its role in promoting tissue repair through angiogenesis and neurogenesis in the border zones of the infarct. Numerous studies, including serial measurements in stroke patients and comprehensive meta-analyses, consistently report elevated VEGF levels in acute ischemic stroke compared to healthy controls, underscoring its potential as a biomarker in cerebrovascular pathologies. The rapid increase in plasma VEGF post-stroke was suggested as a predictor of poor functional outcome in specific stroke subtypes. It was shown to have a positive correlation with neurological severity. Furthermore, elevated VEGF is also found in individuals with stroke risk factors, highlighting its broader involvement in vascular dysfunction.

Regarding TGF, our study demonstrated a significant increase in its levels in ischemic stroke patients (approximately 1.8-fold, $p = 0.0110$). TGF, particularly TGF-Beta, is involved in regulating crucial cellular processes, including cell growth, differentiation, extracellular matrix production, and immune responses, all of which are vital for tissue repair and homeostasis following injury. The observed upregulation of TGF in the border zones of the infarct in other studies suggests a similar role in recovery and improved blood flow. While the literature on TGF levels in acute ischemic stroke is not entirely consistent, with some studies reporting no significant elevation, our finding of an increase supports the hypothesis that TGF is indeed involved in the post-stroke repair mechanisms. The mean TGF level in our ischemic stroke group was notably higher than in the control group, suggesting its potential as a marker for evaluating these repair processes.

According to a peer-reviewed study, serial measurements of VEGF and TGF were performed in 29 patients with acute ischemic stroke, and they were matched with healthy control subjects. VEGF expression was found to be significantly increased in patients. VEGF exhibited a dramatic increase in the serum of stroke patients, but the same was not true for TGF. Pathophysiology of ischemic stroke would indeed be incomplete without acknowledging VEGF (M et al., n.d.); one may conclude that acknowledging VEGF in such vascular pathologies shall not only be an opinion, but rather a fact, based on concrete scientific literature such as a recent study from previous year which examined 112 studies in a meta-analysis to review the relation of 26 fluid bio markers of neurovascular unit (NVU) with cardiovascular and cerebrovascular pathologies, which highlighted the consistent replications of the finding that VEGF was found elevated

(Hansra et al., 2024). This indicated its possible role not only in ischemic stroke patients, but also in patients who suffered from other vascular diseases like cerebrovascular diseases.

According to the literature, the recovery or improvement of blood flow in the region following an ischemic stroke event is determined by angiogenesis, and the expression of TGF-β, VEGF, and PDGF increases in the border zones of the infarcted area (Krupinski et al., 1996). A study on 29 patients in Poland also concluded that researchers found a significant elevation in VEGF levels compared to the control, whereas the same was not true for TGF-beta (Slevin et. al. 2000). The same study implied a significantly high expression of VEGF in patients with a history of ischemic heart disease. VEGF-mediated angiogenesis was successfully targeted for the treatment of angiogenesis and neurogenesis processes in rats that suffered cerebral infarcts (Yang et al., 2015). Plasma VEGF levels increase rapidly after the stroke onset, regardless of which subtype of stroke it is. VEGF value may be considered an independent predictor of poor functional outcome in cardioembolic infarction, as it is positively correlated with neurological severity in these patients (Matsuo et al., 2013). Increased concentrations of VEGF are found in patients with obesity, type 2 diabetes mellitus, hypertension, and coronary artery disease; all of which are significant risk factors associated with stroke, thereby increasing the need for research into its role in the subject of stroke. Five years earlier, there was a lack of prospective studies investigating the possible associations between VEGF concentrations and minor ischemic strokes. However, in September 2020, Chinese researchers from Harbin Medical University published a study examining the utility of VEGF in assessing the 90-day prognosis in patients with minor strokes. The researchers found a significant increase in serum VEGF in stroke patients as compared to control subjects. Besides, serum VEGF levels in patients with cerebral artery stenosis ≥50% were independently associated with an unfavourable outcome (Zhang et al., 2020). VEGF was identified as a major loading factor that discriminated good from poor prognosis after ischemic stroke again in 2020 (Escudero et al., n.d.). VEGFA and VEGFR2 (receptor) showed a clinically significant positive correlation with the modified Rankin scale (mRS) at 3 months in patients of acute ischemic stroke (Hu et al., 2024). In patients who undergo ischemic stroke events, TNF, along with other proinflammatory cytokines (such as IL-6), are released within 24 hours of the injury, and their resulting levels are found to be significantly correlated with stroke severity and poorer prognosis.

Conclusion

In conclusion, the investigation indicates that VEGF/TGF levels are elevated among patients with ischemic stroke compared to healthy controls. These results highlight that VEGF and TGF may be potential and vital indicators of post-stroke repair mechanisms. It would be beneficial to extend the research that may provide insights into developing therapeutic strategies for stroke management. VEGF and TGF may emerge as vital participants in the post-stroke recovery process, highlighting their prospects as therapeutic targets and biomarkers in Ischemic Stroke.

ექსპერიმენტული მედიცინა

VEGF-ისა და TGF-ის შესწავლა იშემიური ინსულტის მქონე პაციენტებში

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იშემიური ინსულტი (IS) მსოფლიოში ერთ-ერთი ყველაზე გავრცელებული ინვალიდობისა და სიკვდილიანობის გამომწვევი დაავადებაა. იშემიური ინსულტის განვითარება დაკავშირებულია მრავალ ფაქტორთან. აღსანიშნავია, რომ ზრდის ფაქტორებს, მათ შორის VEGF-სა და TGF-ს, მნიშვნელოვანი გავლენა აქვს იშემიურ ინსულტზე. ორივე მნიშვნელოვან როლს ასრულებს ნორმალურ ქსოვილში მიმდინარე მრავალი პროცესის წარმართვაში. წარმოდგენილ ნაშრომში შესწავლილია VEGF-ისა და TGF-ის მნიშვნელობა იშემიური ინსულტით დაავადებულ პაციენტებში. TGF-ისა და VEGF-ის დონის შესასწავლად გამოყენებულ იქნა ELISA-ს მეთოდი. სულ შესწავლილია 24 ნიმუში. კერძოდ, საკონტროლო ჯგუფის (ჯანმრთელი) შემთხვევაში 12, იშემიური ინსულტის შემთხვევაში 12 პაციენტი. ექსპერიმენტული მონაცემების სტატისტიკური ანალიზი (აღწერითი სტატისტიკა, t-ტესტი) ჩატარდა GraphPad Prism 10 ვერსიის გამოყენებით. სტატისტიკურად მნიშვნელოვნ მაჩვენებლად განხილულია $p < 0,05$. კვლევამ აჩვენა, რომ VEGF-ის დონე გაზრდილია ~1,5-ჯერ იშემიური ინსულტის მქონე პაციენტებში საკონტროლო ჯგუფთან შედარებით ($p = 0,0474$); რაც შეეხება TGF-ის დონეს, ~1,8-ჯერ გაზრდილია ინსულტის მქონე პაციენტებში საკონტროლო ჯგუფთან შედარებით ($p = 0,0110$). ჩვენი კვლევის მიხედვით, VEGF/TGF დონეები მომატებულია იშემიური ინსულტის მქონე პაციენტებში საკონტროლო ჯგუფთან შედარებით. ვფიქრობთ, რომ VEGF და TGF-თან შეიძლება დაკავშირებულია ინსულტის შემდგომი აღდგენის პროცესის მექანიზმის მნიშვნელოვანი სასიცოცხლო ინდიკატორები. ვფიქრობთ, მნიშვნელოვანია ჩვენი კვლევის გაფართოება, რამაც შეიძლება მოგვცეს დამატებითი ინფორმაცია ინსულტის მართვის თერაპიული სტრატეგიის შემუშავებასთან დაკავშირებულ მნიშნელოვან ასპექტებთან. ამრიგად, VEGF და TGF შეიძლება მნიშვნელოვან როლს ასრულებენ ინსულტის შემდგომი აღდგენის პროცესებში, რაც ხაზს უსვამს მათ გამოყენებას როგორც თერაპიულ, ისე პერსპექტიულ ბიომარკერებს იშემიური ინსულტის მკურნალობის წარმართვის პროცესში.

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