Gremlin-1 in Ischemic Stroke

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Abstract

Objective: Obesity is known to be one of the major risk factors for ischemic stroke. Unexpectedly, there are some studies showing better outcomes in obese stroke patients. Gremlin–1, a protein that inhibits adipogenesis and activates angiogenesis, may be the real biomarker of interest to identify this dilemma. This study was the first to investigate serum Gremlin–1 levels in ischemic stroke patients.

Method: In this cross-sectional descriptive study, patients diagnosed with ischemic stroke by a specialist neurologist and healthy participants as the control group were included. Serum Gremlin–1 levels were measured by the ELISA method and compared statistically.

Results: A total of 87 participants, 49 ischemic stroke patients and 38 controls, were included in the study. The mean age of the stroke patients was 72.1 ± 13.0 years, while the mean age of the control group was 56.9 ± 15.1 years and there was a statistical difference ($p<0.001$). Stroke patients were mostly female (n=27; 55.1%), while the control group was mostly male (n=21; 55.3%), but not statistically different ($p=0.338$). Serum Gremlin–1 levels were 0.672 ± 0.461 ng/mL in stroke patients and 0.762 ± 0.561 ng/mL in the control group. No significant difference was found when compared statistically ($p=0.590$).

Conclusion: Our study is the first to have a look at Gremlin–1 levels in ischemic stroke patients. Gremlin–1 levels were lower in stroke patients, but no significance was found. Further studies are needed in large study groups with time-dependent changes in Gremlin–1 levels.

Keywords: biomarker, Gremlin–1, ischemic stroke

Introduction

Background

Stroke is a serious health problem with an annual incidence of 15 million cases worldwide, causing approximately 5 million disabilities and 5 million deaths (WHO, 2023). Ischemic stroke is defined as an impairment of cerebral blood supply leading to infarction and resulting in neuronal death (Feske, 2021). For the diagnosis of ischemic stroke, computer tomography (CT) should be performed rapidly, and patients should be referred to a stroke center. However, as there are not enough facilities and infrastructure in the world to provide CT scans when needed, and CT scans are expensive and not available in most health centers, there is a need for a practical, simple, and rapid diagnostic tool, a biomarker, for ischemic stroke.

To date, there is no biomarker that can be measured in serum to diagnose an ischemic stroke. The ability to diagnose stroke with a test that can be detected in blood will provide an effective opportunity for diagnosis in health institutions that do not have advanced diagnostic and imaging facilities, such as primary health care centers, or where there is no neurology specialist.

Obesity has an important place among stroke risk factors and studies have shown that each unit increase in body mass index from 20 kg/m^2 leads to a 5% increase in the risk of ischemic stroke (Guzik and Bushnell, 2017). However, many studies have found that obese and overweight patients have lower mortality rates and better functional outcomes after stroke (Forlivesi et al., 2021). This situation has led to conflicting opinions about the relationship between obesity and stroke.

Gremlin–1, a bone morphogenetic protein (BMP)–4 antagonist secreted by TGF-β-activated adipocytes, has been implicated in inflammation, cancer, type 2 diabetes, cardiovascular disease and metabolic disorders, but plays a central role in adipose tissue homeostasis. Gremlin–1 induces pro-inflammatory chemokines, stimulates angiogenesis, acts as an important mediator of tissue fibrosis, and inhibits adipogenesis (Grillo at al., 2023).

The close association of Gremlin–1 with adipose tissue and obesity as a potential stroke risk factor raises the possibility of linking Gremlin–1 to stroke. Since BMP-4 plays a key role in the stimulation and differentiation of adipose tissue, as an antagonist, Gremlin–1 levels must be reduced in order for adipose tissue to be synthesized. Through the roles in inhibiting adipogenesis and activating angiogenesis, Gremlin–1 deserves to be studied in ischemic stroke. However, to the

best of our knowledge, there are no studies in the literature that have looked at Gremlin–1 levels in ischemic stroke patients.

Objective

The aim of the study was to be the first in the literature to determine the level of Gremlin–1 in patients with ischemic stroke and to investigate its use for diagnostic purposes and as a biomarker in ischemic stroke.

Methods

The study was designed as a cross-sectional, descriptive study. Local ethics committee approval was obtained from the university ethics committee with the decision number 04.11.21/07-11 before the study. Informed consent was obtained from the individuals and the criteria of the Declaration of Helsinki were taken into consideration during the study.

Patients over 18 years of age who applied to a university hospital and were diagnosed with ischemic stroke after the necessary evaluation and examinations by a specialist neurologist were included in our study. Healthy individuals over 18 years of age were included as the control group. Pregnant, puerperant, emergency patients, confused and mentally ill patients and participants who did not participate voluntarily were excluded from the study.

Basic demographic characteristics of the stroke patients were obtained and blood samples were taken for the determination of Gremlin–1 levels at the time of admission. Similarly, blood samples were collected from the control group. Serum Gremlin–1 levels were measured biochemically by the ELISA method.

Statistical analysis

The data obtained were statistically analyzed with SPSS 23.0 (IBM, USA) software. Numerical data were presented as mean and standard deviation, whereas categorical data were presented as frequency and percentage. The normal distribution of the data was evaluated by the Shapiro–Wilk test. In the analysis of numerical data, the Student's t–test was used if there was a normal distribution and the Mann-Whitney U test was used if there was no normal distribution. Categorical data were compared by the Chi-square test. For significance, a P value of <0.05 was taken in the entire research.

Results

A total of 87 participants, 49 ischemic stroke patients and 38 controls, were included in the study. The mean age of the stroke patients was 72.1 ± 13.0 years, while the mean age of the control group was 56.9 ± 15.1 years and there was a statistical difference between the groups ($p<0.001$). The majority of stroke patients were female

(n=27; 55.1%), whereas the control group consisted mostly of males (n=21; 55.3%), but there was no statistical difference (p=0.338).

Table 1. Serum Gremlin–1 level comparison of two study groups

	Stroke Group	Control Group
Mean	0.672	0.762
Median	0.710	0.783
Std. Deviation	0.461	0.561
Minimum	0.144	0.024
Maximum	2.294	2.420
Interquartile Range	0.775	0.580

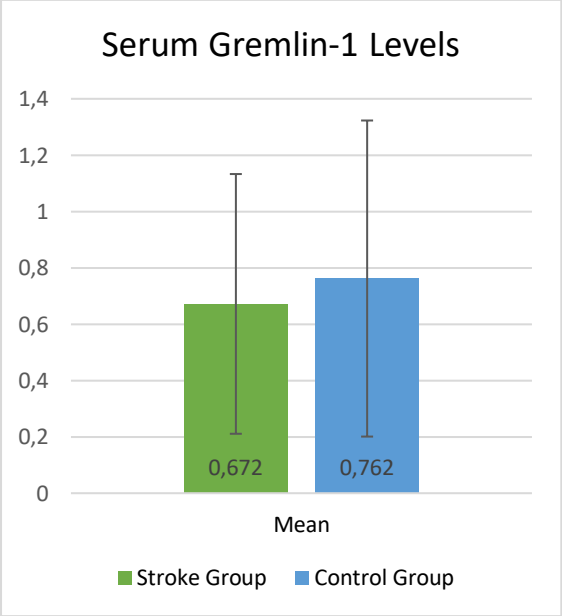

Figure 1. Serum Gremlin–1 levels of study groups

Serum Gremlin–1 levels of the participants included in the study were 0.672 ± 0.461 ng/mL in stroke patients and 0.762 ± 0.561 ng/mL in the control group (Table 1). When compared statistically, no significant difference was found (p=0.590) (Figure 1). As the results were not significant, no further statistical analysis can be performed to identify Gremlin–1 as a biomarker.

Discussion

In our study, serum Gremlin–1 levels were measured for the first time in ischemic stroke patients and compared with the control group. Although the Gremlin–1 level at the time of admission in stroke patients was lower than in the control group, it was not statistically different.

The fact that these data were not found to be significant may be due to the fact that we measured the levels of Gremlin–1 in the stroke patients at the time of their first admission to the hospital. This may be related to the fact that when the serum samples were taken, the clinical picture was still in the early stages, and therefore the mechanisms that would affect the levels of Gremlin–1 were not yet active. It is recommended to investigate the temporal changes in Gremlin–1 levels in future studies. Another possible reason why our study found no difference in Gremlin–1 levels may be that Gremlin–1 was tested in

serum. Tissue or cellular Gremlin–1 levels should be measured to determine the possible differences in serum-tissue levels.

To the best of our knowledge, there is no Gremlin–1 level measurement study in stroke patients in the literature. In an in vitro study conducted by Phani et al. in relation to Parkinson's disease, it was found that Gremlin administration had protective effects against neuronal death (Phani et al., 2013). In an important cell culture study, Gremlin–1 was found to be associated with the development of cortical neuronal cells (Ichinose et al., 2021). In cardiovascular diseases in which Gremlin–1 was studied, it was found that Gremlin–1 levels were increased in myocardial infarction patients, who have similar vascular atherosclerosis ethio-pathogenicity as stroke, and Gremlin–1 levels were found to have protective effects on myocardial functions (Müller et al., 2021). However, in another study investigating Gremlin–1 levels in cardiovascular diseases, it was revealed that intracellular Gremlin–1 levels were associated with acute coronary syndrome and increased serum Gremlin–1 was a mediator in cardiovascular pathophysiology (Chatterjee et al., 2017).

Gremlin–1 levels were found to be elevated in patients with poor glycemic control and positively correlated with body fat (Al-Regaiey et al., 2022). Another study found that Gremlin–1 is responsible for hepatocyte senescence in fatty liver disease, which is associated with a poor prognosis (Baboota et al., 2022). These studies suggest that Gremlin–1 levels are mostly associated with the poor outcomes, and the lower serum levels will be valuable for the follow-up of disease progression. Although our study did not find significance and did not include disease severity, Gremlin–1 levels were lower in ischemic stroke patients, may be the clue for good outcomes. However, the potential relationship between Gremlin–1 and ischemic stroke in terms of disease severity, complications and prognosis remains to be elucidated.

Limitations

Our study has some limitations. Firstly, the study was carried out on a relatively small number of people. Second, the mean ages of the stroke patients included in the study and the control group were statistically different. Since it is not known whether Gremlin–1 serum levels vary with age, it is not known whether our results are affected by this age difference. Third, since we were not interested in the relationship of stroke with obesity, we did not check the BMI or waist circumference of the patients, but Gremlin–1 is associated with the adipose tissue, and therefore being obese or not might have possibly affected the results.

There may also be some confounding factors, such as a history of chronic disease or medication use, that affect Gremlin–1 levels that have not been accounted for. Finally, the we did not look at the progression of serum Gremlin–1 levels, which may be subject to change over time.

Conclusion

In our study, serum Gremlin–1 was measured in ischemic stroke patients for the first time. Although our results were not found to be significant, we hope that further studies may lead to the elucidation of the possible relationship of Gremlin–1 with stroke and that this study may raise awareness.

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