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Value of plasma alpha- and beta-synuclein levels in the diagnosis, severity, and functional outcome of acute ischemic stroke

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Abstract:

OBJECTIVE: We aimed to determine the role of plasma alpha- and beta-synuclein levels and other routine inflammatory parameters in the diagnosis, outcome, and mortality of acute ischemic stroke (AIS).

METHODS: In our study, serum alpha- and beta-synuclein levels and clinical data were prospectively evaluated in 93 subjects (43 controls and 50 AIS patients) admitted to the emergency department. The outcome status and prognostic classification were performed according to the modified Rankin Scale (mRS) scores on the 30th day from hospital admission.

RESULTS: The mean age of the subjects was 70.6 ± 11 years. Thirty-eight percentage were female. Plasma α-synuclein levels in the AIS group (33.6 ± 8.5 ng/mL) were significantly higher than those in the control group (4.22 ± 2.1 ng/mL) ($P < 0.001$). Plasma β-synuclein levels in the AIS group (13.07 ± 2.7 ng/mL) were significantly higher than those in the control group (2.17 ± 1.4 ng/mL) ($P < 0.001$). There was no significant difference in alpha- and beta-synuclein levels between the subgroups formed according to the 30th-day results of the patients using the mRS scores ($P = 0.813$ and 0.812, respectively).

CONCLUSION: The serum alpha- and beta-synuclein concentrations of patients with AIS at admission were significantly higher than the healthy control group. At admission, serum alpha- and beta-synuclein levels do not have definitive clinically predictive value in predicting stroke progression and outcome in patients with AIS.

Keywords:

Acute ischemic stroke, diagnosis, emergency department, Modified Rankin Scale, outcome, synuclein

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Introduction

Acute ischemic stroke (AIS) is known as an urgent medical condition characterized by the sudden and severe disruption of blood flow to a specific region of the brain. This disruption results in a reduction or complete halt of oxygen and nutrient supply to the neurons in the affected area. Typically, this event is brought about by the blockage of a cerebral blood vessel, caused by a blood clot, thrombus, or embolus. The absence of blood flow initiates a series of events, including energy depletion, excitotoxicity, and the release of inflammatory mediators,

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Box-ED section

What is already known on the study topic?

- Acute ischemic stroke (AIS) is defined as a sudden flow disturbance in the arteries that provide blood supply to the brain and the resulting sudden loss of brain function
- As soon as possible, AISs should be diagnosed, and recanalization of the problematic artery(s) is essential. In patients with delayed or no recanalization, irreversible brain damage and loss of function occur.
- Computed tomography (CT) angiography and diffusion magnetic resonance imaging (MRI) are diagnostic modalities in the current ischemic stroke management. There is no specific blood biomarker used in routine stroke diagnosis.

What is the conflict on the issue? Has it importance for readers?

- The most important problem in current ischemic stroke management is delayed patient treatment due to the lack of diagnostic tests or the prolonged duration of these tests
- The use of a specific blood biomarker for AIS will accelerate the diagnosis and treatment of patients. It will also provide an important diagnostic convenience for centers without CT or MRI facilities.

How is this study structured?

- This is a single-center, prospective, and methodological study, including clinical and laboratory data of 93 subjects. In the study, the relationship between AIS and serum alpha- and beta-synuclein levels is evaluated.

What does this study tell us?

- The serum alpha- and beta-synuclein concentrations of patients with AIS at admission were significantly higher than the healthy control group.
- However, at admission, serum alpha- and beta-synuclein levels do not have definitive clinically predictive value in predicting stroke progression and outcome in patients with AIS.

ultimately leads to the swift death of brain cells within the impacted region.[1-5]

The high mortality, morbidity, and disability rates in AIS patients necessitate early diagnosis and rapid restoration of cerebral perfusion.[2,4,6] The diagnostic imaging and clinical evaluation disciplines currently in use may be insufficient to start the treatment of the patient as soon as possible due to factors such as the need for a physician with sufficient experience. Limitations in access to imaging in small health institutions and time-consuming examinations make this situation more important. Based on this problem, many studies have been conducted in the literature on new-generation clinical scoring systems, laboratory parameters, and imaging methods.[4,5,7-11] Predictive and prognostic factors play a crucial role in AIS, offering valuable insights into the potential course of the disease and aiding in treatment decision-making. Identifying robust prognostic indicators allow health-care professionals to tailor interventions based on individual patient characteristics, optimizing therapeutic strategies, and resource allocation. Researchers actively seek to discover novel predictive and prognostic biomarkers to enhance our understanding of the disease's trajectory and improve patient outcomes. Advances in this field contribute not only to refining prognostic models but also to the develop targeted therapies, ultimately paving the way for more personalized and effective management of AIS.[1,7-10]

Alpha-synuclein, beta-synuclein, and gamma-synuclein constitute members of the synuclein protein family, as documented in scientific literature. Notably, gamma-synuclein is predominantly expressed in the peripheral nervous system, whereas alpha- and beta-synucleins are predominantly expressed in the central nervous system, particularly in neurons.[12,13] The roles of alpha-synuclein and beta-synuclein in the context of AIS remain incompletely understood, and their specific contributions to this condition are not clearly described.[14] Numerous preclinical investigations into synucleins concerning AIS have primarily centered on their detection in cerebrospinal fluid or brain tissues, with less emphasis on blood. These studies frequently investigate the potential utility of synucleins as biomarkers for various neurological disorders, including stroke.[15-18] The potential use of alpha-synuclein levels in the bloodstream as a biomarker after AIS was first suggested clinically in 2019.[14] Furthermore, no studies have specifically investigated the comparison of blood levels of both alpha-synuclein and beta-synuclein in the context of AIS within clinical settings. In our study, we aimed to investigate the role of plasma alpha- and beta-synuclein levels in the diagnosis, prognosis, and mortality of AIS.

Methods

Study design, population, and participants

Fifty patients with AIS with a definite diagnosis of AIS, made both clinically and radiologically (by head computed tomography [CT] or magnetic resonance imaging [MRI]), who were admitted to the Emergency Department (ED) at University Medical School Research Hospital in a period of 6 months, and 43 healthy volunteers with similar age and sex ratios to the patient group were included in this prospective methodological study.

In the power analysis (G*Power 3.1.9.4 package program), the sample size of each of the control and experimental groups was determined as a minimum of 12 for 80% power, a minimum of 16 for 90% power, and a minimum of 20 for 99% power with an effect size of 1.86 at 95% significance level.

Inclusion criteria for the study were AIS (≤12 h after onset of stroke symptoms) over 18 years of age and consent to be included in the study. Subjects with a history of stroke, acute hemorrhagic stroke in pregnancy, conditions that will affect synuclein levels (peripheral vascular disease, cancer, chronic hepatobiliary or renal insufficiency, immune system disease, etc.), nonsteroidal anti-inflammatory drugs, history of corticosteroid use before admission, and National Institutes of Health Stroke Scale (NIHSS) score could not be calculated at the time of admission or refusal to participate were excluded.

Healthy volunteers, similar to the patient cohort in terms of age and gender, were included into the study as a control group. Thus, this case–control study included a total of 93 participants, 50 patients with AIS and 43 healthy volunteers.

Ethics statement

Ethical approval for this study was obtained from Trakya University Faculty of Medicine Scientific Research Ethics Committee (Date: 24/08/2020 52 and Protocol no: TUTF-BAEK 2020/283). The Declaration of Helsinki was fully complied, and the data required to protect patient privacy were obtained from clinical records without any clinical intervention. Participation in the study was consented in writing by the patients or their relatives and healthy volunteers.

Data collection and outcome evaluation

This study collected clinical data, including baseline information: age, gender, vital parameters, NIHSS, Glasgow Coma Scale score, history of hypertension, coronary heart disease, diabetes, and duration from symptom onset to hospitalization (≤4, 5 h, >4, 5 h) on admission. All patients were followed up until the end of 30 days by outpatient visits or telephone meetings. The outcome status of the patients on the 30th day was recorded by calculating the Modified Rankin Scale (mRS) scores. Prognostic classification was performed according to these scores. The results of outcomes were classified as good outcome (mRS score of 0–2), poor outcome (mRS score of 3–5), and death (mRS score of 6) at 1-month mRS (30 days) from hospital admission. All patients were examined by head CT and MRI; the area of cerebral infarction was determined, and the results were recorded as middle cerebral artery (MCA), posterior cerebral artery (PCA), anterior cerebral artery (ACA), and others.

Evaluation of laboratory parameters

Clinical laboratory data were collected in the ED during admission to the hospital. Laboratory data were obtained from the information operating system of our hospital and recorded on the study form.

For alpha-synuclein and beta-synuclein, 3 mL of venous blood sample was collected on the shelf of the cooler in the ED at + 4°C for 24 h and then centrifuged at + 4°C for 20 min at a speed of 2000 rpm in a centrifuge with cooling feature in the ED. After the procedure, at least 300 µl of serum were placed in an Eppendorf tube and kept in the cooler in the central laboratory of the hospital at 73°C until the study day. Serum samples were taken out of the freezer 1 day before the study and thawed at room temperature. Then, alpha-synuclein and beta-synuclein serum levels were measured by sandwich enzyme-linked immunosorbent assay (ELISA) method in the hospital biochemistry department laboratory using human SNCa ELISA kit 201-12-5050 serial number and human SNCb ELISA kit 201-12-5051 serial number of Shanghai Sunred Biological Technology Co.

Statistical analysis

For data analysis, SPSS for Windows 27.0 (SPSS Inc., Chicago, IL, USA, serial number: 10240642) version was used. The Kolmogorov–Smirnov test was used to analyze whether the variables were normally distributed. To analyze categorical variables, Pearson's Chi-square and Fisher's exact were used. Categorical data were presented as number (n) and percentage (%); continuous data with normal distribution were presented as mean ± standard deviation. To evaluate the significant difference between the two independent groups, the Mann–Whitney *U*-test was used for nonnormally distributed data, and the Student's *t*-test was used for normally distributed data. Comparison of more than two categorical groups and continuous variables: if the data were normally distributed, they were analyzed by one-way analysis of variance test (*post hoc* test was Tukey), and if they were not normally distributed, they were analyzed by Kruskal–Wallis H-test (*post Hoc* test was Tamhane's T2). Sensitivity, specificity, positive and negative predictive values, and usability in relation to stroke mortality were assessed using receiver operating characteristic (ROC) curve analysis. Results with $P < 0.05$ were considered statistically significant.

Results

During the study period, 50 AIS patients presented to the ED. The mean ages of the patient and control groups were 70.6 ± 11.1 years (min–max: 51–93 years) and 70 ± 10.1 years (min–max: 50–91 years) ($P = 0.970$). Thirty-one (62%) of the patient group was male. Twenty-six (52%) patients presented to the ED within

the first 4, 5 h after onset of AIS symptoms, mostly presented with two neurological symptoms. Descriptive characteristics of the patient group are shown in Table 1.

The severity of the stroke was evaluated on admission using NIHSS. The mean NIHSS was 9,3 ± 7,5. The most common area of stroke, as detailed by CT angiography, was the MCA (50%). This was followed by the ACA (6%) and PCA (6%). The remaining patients had stroke in other areas (38%).

Plasma α-synuclein levels in the AIS group (33.6 ± 8.5 ng/mL) were significantly higher than those in the control group (4.22 ± 2.1 ng/mL) ($P < 0.001$). Plasma β-synuclein levels in the AIS group (13.07 ± 2.7 ng/mL) were significantly higher than those in the control group (2.17 ± 1.4 ng/mL) ($P < 0.001$) [Table 1].

Table 1: Patient–control groups descriptives and alpha-/beta-synuclein levels

	Patient (*n*=50), *n* (%)	Control (*n*=43), *n* (%)	*P*
α-synuclein (ng/mL), mean±SD	33.6±8.5	4.22±2.1	<0.001*
β-synuclein (ng/mL), mean±SD	13.07±2.7	2.17±1.4	<0.001*
Age (years), mean±SD	70.6±11	70±10.1	0.97
Gender			
Female	19 (38)	16 (37)	0.938
Male	31 (62)	27 (63)	
Admission to hospital (h)			
<4.5	26 (52)	-	-
≥4.5	24 (48)	-	
Comorbidities			
Hypertension	22 (44)	-	-
Coronary artery disease	19 (38)	-	-
Diabetes mellitus	13 (26)	-	-
Cerebrovascular disease	15 (30)	-	-
Other	17 (34)	-	-
Vital parameters, mean±SD			
Systolic blood pressure (mmHg)	141.3±32.5	127.3±8.3	0.043*
Diastolic blood pressure (mmHg)	79.8±20.4	80.1±7.2	0.63*
Pulse rate (/min)	91.4±17.9	80.3±5.1	0.036*
Fever (°C)	36.3±0.2	36.1±0.3	0.875*
Respiratory rate (/min)	17±2.7	16±4.3	0.125*
GCS (admission)	13.6±1.4	15	0.03*
NIHSS, mean±SD	9.3±7.5	-	-
Infarct area			
ACA	3 (6)	-	-
MCA	25 (50)	-	-
PCA	3 (6)	-	-
Other	19 (38)	-	-
mRS at 30th day			
Mild (0–2)	20 (40)	-	-
Moderate–severe (3–5)	17 (34)	-	-
Exitus (6)	13 (26)	-	-

*Student's *t*-test. mRS: Modified Rankin Scale scores, NIHSS: National Institutes of Health Stroke Scale, SD: Standard deviation, MCA: Middle cerebral artery, PCA: Posterior cerebral artery, ACA: Anterior cerebral artery, GCS: Glasgow Coma Scale score

Alpha- and beta-synuclein levels were compared depending on admission time. The mean alpha-synuclein levels of patients with admission time <4.5 h were significantly lower than those with admission time longer than 4.5 h (31.0 ± 7.8 and 36.6 ± 8.4, respectively, $P < 0.05$). However, no significant difference was found between the groups in terms of mean beta-synuclein levels (12.9 ± 2.8 and 13.2 ± 2.6, respectively, $P > 0.05$).

30th day Modified Rankin Scale analysis

mRS evaluated a stroke's prognosis and functional recovery at 1 month. Patients were divided into three groups as good outcome (n = 20, %40), poor outcome (n = 17, %34), and death (n = 13, %26).

There was no significant difference in alpha- and beta-synuclein levels between the subgroups formed according to the 30th-day results of the patients using the mRS scores (P = 0.813 and 0.812, respectively) [Table 2]. It was observed that those with a hospital arrival time of more than 4.5 h resulted in higher mRS than those with less time ($P < 0.001$) [Table 2].

Mortality analysis

Mortality occurred in 26% (n = 13) of patients with AIS during the 1st month. Patients were divided into two groups according to the presence of mortality during the 1-month observation period and alpha- and beta-synuclein levels, and other data thought to be effective in mortality were analyzed in these two groups. Demographic, clinical, and laboratory differences between dead and surviving patients are given in Table 3. ROC curve analyses were performed to determine the cutoff value, sensitivity, and specificity of the α- and β-synucleins for mortality [Figure 1 and Table 4].

Discussion

It is an important fact that glial or neuronal proteins that can be used as biomarkers can easily cross the blood–brain barrier and be detected in peripheral blood early after an acute ischemic attack. Ideal acute stroke biomarkers that can be used in practice should be released early in the infarct, have the potential for risk assessment, guide therapies, and be quantitatively and rapidly measured by cost-effective methods. Furthermore, ideal stroke biomarkers should be diagnostically sensitive and specific to the infarct. The roles of alpha-synuclein and beta-synuclein in the context of AIS remain incompletely understood, and their specific contributions to this condition are not clearly defined. Numerous preclinical investigations into synucleins concerning AIS have primarily centered on their detection in cerebrospinal fluid or brain tissues, with less emphasis on blood. These studies frequently investigate the potential utility

Table 2: α- and β-synuclein levels according to prognosis groups

Parameters	Patient prognosis groups (mRS) (30th day), mean±SD			*P*		
	Group 1 (good outcome) - (0–2); *n*=20	Group 2 (poor outcome) - (3–5); *n*=17	Group 3 (death) - (6); *n*=13	1–2	2–3	1–3
α-synuclein	32.92 ± 7.21	32.90 ± 10.27	32.85 ± 6.3	0.813*		
β-synuclein	12.26 ± 1.39	13.64 ± 3.42	13.43 ± 2.89	0.812*		

*ANOVA test. mRS: Modified Rankin Scale scores, SD: Standard deviation

Table 3: α- and β-synuclein levels according to mortality

Parameters	Mortality		*P*
	Survived group (*n*=37)	Died group (*n*=13)	
α-synuclein	31.99 ± 17.9	33.17 ± 9.7	0.83*
β-synuclein	12.02 ± 1.6	12.65 ± 3.7	0.57*

*Student's *t*-test

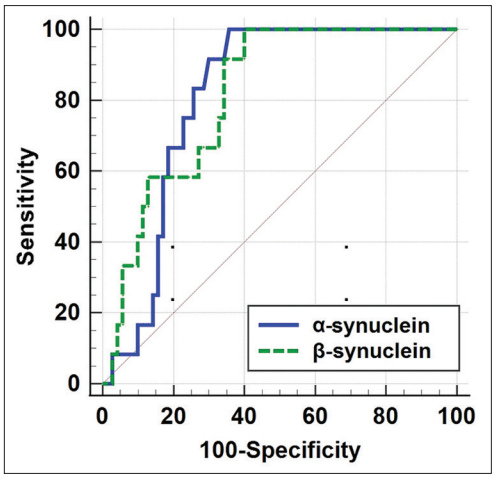

Figure 1: Receiver operating characteristic of α-and β-synucleins for mortality

of synucleins as biomarkers for various neurological disorders, including stroke.[14,16,18]

Recent investigations have unveiled the pathogenic roles of alpha-synuclein in traumatic and vascular disorders of the central nervous system, including traumatic spinal cord injury, brain injury, and stroke, exacerbating neurodegenerative processes.[18,19] Furthermore, studies have shown that alpha-synuclein mediates ischemic brain damage. Knockdown of alpha-synuclein has been demonstrated to significantly reduce poststroke brain damage and enhance motor function recovery in both adult and aged mice of both sexes.[13] Hu *et al*.[20] reported that synuclein levels were found to be significantly higher in the cerebral cortex tissue of rats in a model of cerebral ischemia induced by carotid artery ligation in rats. Despite these findings, the mechanism underlying the aggregation of alpha-synuclein remains uncertain. The potential use of alpha-synuclein levels in the bloodstream as a biomarker after AIS was first suggested clinically in 2019.[14]

In two distinct clinical studies reported in 2021 and 2023, the relationship between serum levels of beta-synuclein and ischemic stroke was evaluated.[15,16] O'Connell *et al*.[15] demonstrated an association between beta-synuclein serum levels in 43 patients and the extent of neural tissue damage in ischemic stroke. Barba *et al*.[16] conducted a clinical assessment of the prognostic value of serum beta-synuclein in 30 adult patients with moderate-to-severe AIS at the 3-month follow-up. Research into the specific role of beta-synuclein in AIS is limited, necessitating further studies to comprehensively understand its functions in this particular context.

Barba *et al*.[16] proposed that beta-synuclein levels were significantly and positively correlated with the risk of death attributed to severe neurological complications. Nevertheless, our findings suggest a strong association between blood levels of both alpha- and beta-synuclein and AIS. Notably, no significant correlation was observed between the measured synuclein levels and the prognosis of the disease, as indicated by mRS scores at 1 month. This lack of correlation may be attributed to the 30-day duration of our study and potential demographic differences.

Furthermore, no studies have specifically investigated the comparison of blood levels of alpha-synuclein and beta-synuclein in the context of AIS within clinical settings. In our study, we investigated the efficacy of alpha-synuclein and beta-synuclein, which may be new biomarkers that can rapidly and accurately diagnose stroke. Hence, that treatment can be initiated early in acute ischemic cases, thus reducing morbidity and mortality.

In our study, we aimed to prevent potential errors in terms of results by including healthy volunteers similar to the patient group in terms of age and gender. The rates of comorbidities in the sample were consistent with the literature.[2] The MCA is the most common artery involved in acute stroke. In our study, when the infarct areas of the patient group were evaluated, infarction was most frequently observed in the area supplied by the MCA, consistent with the literature.[1,2,21]

In terms of the decision for rapid recanalization therapy, another valuable factor is the time, and it takes for the patient to reach the hospital. According to this period, thrombolytic or thrombectomy decision is taken. In our study, we evaluated synuclein levels

Table 4: Optimal cutoff levels determined for mortality based on receiver operating characteristic analysis

	Cutoff	AUC	CI (%)	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
α-synuclein	>22.79	0.818	0.720–0.894	100	63.9	100	33.3
β-synuclein	>4.79	0.815	0.714–0.893	100	60	100	30

CI: Confidence interval, AUC: Area under the curve, NPV: Negative predictive value, PPV: Positive predictive value

in terms of the time from the onset of the patient's complaints to the hospital admission. We found that alpha-synuclein increased in parallel with the time to reach the hospital, whereas beta-synuclein did not show such a significant increase. Based on these results, it can be concluded that alpha-synuclein is superior in the evaluation of the amount of ischemic damage and the recanalization treatment decision. We believe that these results may be the starting point for more comprehensive studies.

The mRS was used to create groups for disease outcome and prognosis.[1,3,5] In our study, patients were grouped as good functional outcome, poor functional outcome, and death by calculating the modified Rankin score according to 30-day follow-up results. In the study by Oray *et al*.,[4] it was reported that patient age was associated with poor outcome according to mRS, but in our study, no significant correlation was observed between age and patient outcome. This difference may be due to the demographic characteristics of the study groups and variations in the number of samples. Studies in the literature have reported significantly worse functional recovery and lower quality of life in women after stroke compared to men.[22] In the study by Sun *et al*.,[10] gender difference did not show a significant difference in terms of disease outcome. Similarly, no significant difference was found between genders in terms of disease outcome in our study. Seno *et al*.[23] reported that an increase in the time from the onset of complaints to the time of hospitalization would increase the functional loss of patients. In our study, a compatible result was obtained.

Limitations

There are several limitations in our study. First of all, this study was designed in a single center with a small cohort size. Some results may differ between different populations. The results should be confirmed in future multicenter studies with large samples. In this study, serum samples were collected only at the time of presentation. Multiple dynamic measurements should be performed at different periods of the disease to obtain more reliable results. In addition, this study followed 30-day survival and functional outcomes of patients with AIS. Long-term follow-ups such as 3 months and 12 months were not included in the study. Therefore, the effects of serum alpha- and beta- synuclein levels on long-term survival and functional outcomes could not be determined.

Conclusion

The serum alpha- and beta-synuclein concentrations of patients with AIS at admission were significantly higher than the healthy control group. At admission, serum alpha- and beta-synuclein levels do not have definitive clinically predictive value in predicting stroke progression and outcome in patients with AIS.

Additional investigations are necessary to delineate the precise roles of these synucleins in the pathophysiology of AIS and to pinpoint potential therapeutic targets. To summarize, although alpha- and beta-synucleins exhibit certain structural and functional similarities, their distinctions in terms of aggregation propensity, biological function, and genetic associations underscore their unique roles in normal cellular function and potential contributions to neurodegenerative diseases. Comprehensive research is essential to fully unravel the intricate mechanisms governing their participation in neurodegeneration.

We think that future studies with larger samples, multicenter, and sequential sampling may more clearly demonstrate the value of alpha- and beta-synuclein in the diagnosis and prognosis of patients with AIS.

Author contributions

Conceptualization – MBS, OBF
Data curation – OBF, ID
Formal analysis – OS, AY
Investigation – OBF, OS, ID
Methodology – MBS, OS, OBF
Project administration – OBF, OS
Resources – OBF, OS
Software – AY, MBS
Validation – MBS, OS, ID
Visualization – OBF, MBS, AY
Writing – original draft – OBF, OS
Writing – review and editing – MBS, OBF, AY.

Conflicts of interest

None Declared.

Ethical approval

Approval for this study was obtained from Trakya University Faculty of Medicine Scientific Research Ethics Committee Date: 24/08/2020 and Protocol no: TUTF-BAEK 2020/283. We declare that we comply with the rules of research and publication ethics.

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