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Is there a relationship between NR-2 antibody peptide level and diagnosis, prognosis and coma scores in acute ischemic stroke?

NR-2 antikor peptid düzeyinin akut iskemik inmede tanı, prognoz ve koma skorları ile ilişkisi var mıdır?

Alpay Tuncar[1]*, Basar Cander[1], Kadir Kucukceran[1], Fatma Humeyra Yerlikaya[2]

1.Necmettin Erbakan University, Medical Faculty, Department of Emergency Medicine, Konya, Turkey
2.Necmettin Erbakan University, Medical Faculty, Department of Biochemistry, Konya, Turkey

ABSTRACT

Aim: This study aimed to demonstrate the diagnostic and prognostic value of NR-2 peptides as a biomarker in acute ischemic stroke and to evaluate their correlation with the Glasgow Coma Scale (GCS) and the National Institutes of Health Stroke Scale (NIHSS).
Materials and Methods: The importance of NR-2 peptide level in diagnosis and prognosis in acute stroke was investigated cross-sectional and prospectively. The study included 101 patients, who presented to a tertiary healthcare facility and were diagnosed with acute stroke, and 57 healthy controls. In the whole study population, serum NR-2 peptide levels were measured using the ELISA method.
Results: The NR-2 peptide level was 6.32 ± 8.30 in the patient group and 3.91 ± 1.64 in the study group. The NR-2 peptide level was significantly higher in the patient group (p = 0.006). No correlation was detected between NR-2 peptide levels and scores in the GCS or NIHSS. The results indicated that NR-2 was a potential biomarker elevated in the early phase of acute stroke, but had no correlation with the prognosis of acute stroke.
Conclusion: Although our data shed light on the use of the NR-2 peptide level as a biomarker in the acute phase in patients with stroke, data are insufficient to predict prognosis. We think that larger, multicenter studies with longer follow-up periods are needed.

Key words: Stroke, NR-2 peptide, diagnosis, prognosis, biomarker

ÖZ

Amaç: Bu çalışmanın birincil amacı akut iskemik inme'de biyobelirteç olarak NR-2 peptidinin tanısal ve prognostik değerini göstermek, ayrıca Glasgow koma skoru (GKS) ve Ulusal Sağlık Enstitüleri İnme Ölçeği (NIHSS) arasındaki ile ilişkisinin araştırılmasıdır.
Yöntemler: Akut inme de NR-2 peptid düzeyinin tanı ve prognozdaki önemi prospektif kesitsel olarak araştırılmıştır. Çalışmaya üçüncü basamak sağlık kuruluşuna bir yıl içerisinde başvurup akut inme tanısı kesinleşen 101 hasta ve 57 sağlıklı kontrol grubu alınmıştır. Tüm çalışma grubunda serumda NR-2 peptid düzeyi ELISA yöntemi ile ölçülmüştür. Elde olunan sonuçlar hastaların prognoz kriterini öngörebilecek olan koma skorlamaları ile ilişkisine bakılmıştır.
Bulgular: Elisa yöntemi ile ölçülen NR-2 peptid düzeyi hasta grubunda 6,32±8,30, kontrol grubunda 3,91±1,64 saptandı. NR-2 düzeyi hasta grubunda daha yüksek olup istatistiksel olarak anlamlı fark vardır (p:0,006). NR-2 düzeyi ile GKS ve NIHSS arasında ilişki saptanmamıştır. Bu sonuçlar ile NR-2 düzeyi akut inmede erken dönemde yüksek saptanılan potansiyel bir biyobelirteç olmasına karşın bu protein düzeyinin akut inme prognozu ile ilişkisi saptanmadı.
Sonuç: Sonuçlarımız NR-2 düzeyinin inmeli hastalarda biyomarker olarak akut dönemde kullanılabilmesi için ışık tutmakla birlikte, hastalığın prognozunu öngörmede yeterli verilere sahip değildir. Bu konuda daha fazla hasta popülasyonu ile çok merkezli, hastaların daha uzun süre takip prognozlarının izlenildiği çalışmalara ihtiyaç olduğunu düşünmekteyiz.

Anahtar kelimeler: İnme, NR-2 peptidi, tanı, prognoz, biyobelirteç

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*Corresponding Author: Alpay Tuncar, Department of Emergency Medicine, Necmettin Erbakan University, Medical Faculty, Konya, Turkey. +905325058127 dralpaytuncar@gmail.com

ORCID ID: 0000-0002-3889-819X

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INTRODUCTION

Stroke is the second leading cause of disability and death worldwide. Early diagnosis is essential to ensure appropriate and timely management [1]. Although clinical findings diagnose stroke, it is important to define and categorize it [2]. Approximately 80% of strokes are ischemic, while 15 to 20% is hemorrhagic, with different therapeutic and prognostic outcomes. Specific management and treatment protocols recommend thrombolysis in stroke subtypes, including blood pressure control [2]. Although imaging is a mainstay for discriminating ischemic stroke (IS) from intracerebral hemorrhage (ISC), it is not always available. In stroke, biomarker studies rely on pathophysiological aspects of ischemic tissue injury and the likelihood of elevated serum protein levels after tissue injury. There may be some biomarkers secondary to hemostasis, endothelial injury and tissue damage in this process. High-resolution screening of many molecules is another way to identify a biomarker. Other methods include genome and proteomic approaches and RNA expression [3,4]. However, the limitations of biomarkers result from the fact that tissue injury may develop over time, and the blood-brain barrier may hamper the release of these molecules into circulation.

Recently, biomarkers have gained increasing interest, with groups focusing on discovering an optimal biomarker for a certain disease worldwide. Some proteins are promising biomarkers, but there is a deficiency in specificity and sensitivity. In previous studies, several aspects of stroke, including diagnosis, severity, outcome, etiology and correlation, were investigated using biomarkers such as astroglial protein S100B, glial fibrillary acidic protein (GFAP), neuron-specific enolase (NSE) and vascular cell adhesion molecule (VCAM)-1. Although results were promising for intercellular adhesion molecule (ICAM)-1, N-methyl-D aspartate (NMDA) receptor antibodies and matrix metalloproteinases (MMPs), as well as acute thrombosis molecules, such as D-dimer and von-Willebrand factor (vWF), none was found to be absolute or specific. However, these biomarkers can reflect the severity of sub-acute or established stroke [5,6]. The lack of a relationship between these biomarkers and stroke may be translated as the blood-brain barrier limiting their release into systemic circulation; thus, they do not correlate with stroke severity [5]. However, clinicians seek a biomarker with predictive value as soon as possible [6]. NMDA receptor peptides and their auto-antibodies (NR-2Ab) have been proposed as biomarkers for neurotoxicity underlying cerebral ischemia and stroke [7]. Anti-NMDA IgG receptor antibodies are formed in response to the release of peptide fragments derived from the NMDA receptor cycle and have long been identified in the sera of stroke patients [7-9]. These antibodies were found in the sera after stroke and remained elevated for months. The preoperative serum concentrations of NR-2Ab may herald severe neurological adverse events. It was found that the likelihood of experiencing postoperative neurological adverse events was 18-fold higher in patients with positive NR-2 antibodies (>2.0 ng/mL) than in those with negative antibodies [10].

This study aimed to demonstrate the diagnostic and prognostic value of NR-2 peptides as a biomarker in acute ischemic stroke and to evaluate their correlation with the Glasgow Coma Scale (GCS) and the National Institutes of Health Stroke Scale (NIHSS).

MATERIALS AND METHODS

Study design

This cohort study measured and compared NR-2 peptide levels in patients with confirmed stroke and controls. The local scientific research projects unit approved it with project number 2014/575/141518022.

Study population

The study included 101 patients (aged >18 years) who presented within 72 hours after onset of acute stroke symptoms and 57 healthy controls without a diagnosis of acute stroke, between February 2014 and February 2015. Patients with hemorrhagic stroke, vascular dementia, hypertensive encephalopathy, pregnancy, were breastfeeding, had chronic renal disease, chronic liver disease, chronic heart failure and an acute transient ischemic attack, were all excluded. In addition, patients with blood sample hemolysis

were also excluded due to the potential for cross-reaction with hemoglobin. Written informed consent was obtained from all subjects (patients and controls) or first-degree relatives.

In patients with a clinical diagnosis of stroke, blood samples (5 ml) were drawn into EDTA vacuum tubes and placed in ice blocks. The samples were centrifuged within 30 minutes to consume the NR-2 peptide by serine proteases. The plasma was obtained by centrifugation at 4000 rpm over 4 minutes, and the samples were transferred to Eppendorf tubes and stored at -80°C until assays. After collecting blood samples from all subjects, NR-2 analysis was performed by a blinded researcher, in accordance with the manufacturer's instructions, at the biochemistry laboratory. In addition, blood samples for routine laboratory evaluations (complete blood count, biochemical assays and coagulation parameters) were obtained from all subjects.

ELISA procedure

Following the manufacturer's instructions, the serum antibody concentrations were measured using the Gold Dot NR-2 Antibody Test (CIS Biotech, Inc., Atlanta, GA). Briefly, 100 µl diluted serum (1:50; 20 µl serum sample +980 µl diluent) and calibration sets were placed into NR-2-coated microtiter plates and incubated in a shaker for 30 minutes at 37°C. The wells were washed using buffer, then 100 µl of protein A-HRP-labelled antibody was added, and the mixture was incubated in a shaker for 30 minutes at 37°C. After 100 µl, a ready-to-use TMB substrate was added. NR-2Ab titter was calculated using standards provided by the Gold Dot NR-2 antibody test in each sample.

Clinical evaluation

Physical examination, neurological examination, history and standard neurological stroke examination were performed on all patients. In all patients diagnosed with a stroke, standard neurological and physical examinations were performed using NIHSS and GCS [11,12]. All stroke patients underwent immediate CT scans, and MR imaging was obtained within 24 hours. An experienced neurologist examined all patients during admission. Clinical definitions were made before the N2Ab measurement. All controls, medical history, risk factors for stroke, medication and previous strokes were recorded using a questionnaire.

Magnetic resonance imaging and analysis

The MR images were captured by a standard MRI device using single-pulse echo-linear gradients. The standard dataset included T1-weighted sagittal sequences, diffusion-weighted sequences, visible diffusion coefficient, FLAIR and T2-weighted images.

Statistical analysis

All statistical analyses were performed using the SPSS version 20.0 (IBM Corp., Armonk, NY, USA). The normal distribution was tested for numerical variables. The Wilcoxon sign test was used in dependent groups. The Kruskal-Wallis test was used in more than two independent groups, while the Mann-Whitney U test was used in more than two independent groups with skewed distribution. Correlation analyses were performed using Pearson's and Spearman's correlation tests for numerical variables. A p-value of <0.05 was considered statistically significant.

RESULTS

Table 1 presents the demographic characteristics of patients (n = 101) and controls (n = 57). The NR-2 peptide level was 6.32 ± 8.30 in the patient group and 3.91 ± 1.64 in the study group. The NR-2 peptide level was significantly higher in the patient group (p = 0.006). Table 2 compares NR-2 peptide levels and laboratory evaluations between the groups. No correlation was detected between NR-2 peptide levels and GCS or NIHSS scores (r = -0.666, p = 0.001). Table 3 presents the results of the correlation analyses.

DISCUSSION

To the best of our knowledge, this study is the first to compare biomarker levels and neurological coma scales, although there are many biomarker studies on stroke in the literature.

Biomarkers offer the opportunity for both acute stroke detection and prediction of stroke risk. However, no optimal biomarker for ischemia and stroke has been defined. In the case of

Table 1: Demographics and patient characteristics of the patient and control groups, vital signs

Parameters	Patient (n=101)	Control (n=57)	p- value
Age(years)	72.35±13.33	62.95±15.41	0.001
Gender (%male)	42/101(45.5)	32/57(70)	0.133
Body temperature (°C)	36.52±0.33	37.5±15.6	0.219
Pulse (/ minute)	83.28±20.03	90.72±18.19	0.006
Systolic blood pressure (mmHg)	144.7±31.3	137.1±28.9	0.134
Diastolic blood pressure (mmHg)	84.8±17.7	82.4±14.4	0.47

*p < 0.05 is considered as significant

Table 2: Comparison with laboratory values between groups

Parameter	Patient Group	Control Group	p value
NR-2 (ng/dl)	6.32±8.30	3.91±1.64	0.006
Hgb (gr/dl)	13.51±1.88	13.59±2.63	0.832
Hct (%)	40.23±6.38	41.61±7.73	0.228
Rbc (106/uL)	4.66±0.60	4.79±0.85	0.296
Wbc (103/uL)	9.33±3.25	9.41±4.46	0.901
Neutrophil (103/uL)	6.65±3.13	7.01±4.15	0.542
Lymphocyte (103/uL)	1.91±0.85	1.76±1.15	0.358
Plt (103/uL)	251.07±66.84	251.28±93.01	0.988
PT (sec)	14.27±1.84	16.86±4.59	0.016
İNR (iu)	1.11±0.19	1.38±0.50	0.152
PTT (sec)	30.15±6.67	27.05±4.68	0.227
Glucose (mg/dL)	140.37±62.79	151.53±88.35	0.402
Urea (mg/dL)	45.40±21.08	37.61±19.62	0.024
Creatinine (mg/dL)	1.54±6.79	0.87±0.53	0.463
Sodium (mmol/L)	139.14±3.58	137.82±4.18	0.039
Potassium (mmol/L)	4.33±0.63	4.58±0.65	0.019
AST (u/L)	36.53±74.46	26.11±10.67	0.170
ALT (u/L)	27.30±58.83	20.77±18.22	0.416
CKMB (ng/ml)	3.92±7.56	3.69±6.75	0.864
Troponin-I (ng/ml)	0.04±0.09	0.02±0.02	0.077

Table 3: Comparison of GKS, NIHSS and NR-2 peptide value

		GKS	NR-2	Volume	NIHSS
NR-2	r	-0.073	1	-0.070	0.053
	p value	0.470		0.493	0.597
	n	101	101	99	101
GKS	r	1	-0.073	-0.102	-0.666
	p value		0.470	0.315	0.001
	n	101	101	99	101
NIHSS	r	-0.666	0.053	0.290	1
	p value	0.001	0.597	0.004	
	n	101	101	99	101

r: correlation coefficient NR-2: NR-2 peptide (ng/dl), Volume: volumetric measurement values (cm3), NIHSS: National Institutes of Health Stroke Scale, GKS: Glasgow coma scale,

a stroke, available diagnostic tests, including MR imaging with or without diffusion-weighted images, may provide inadequate diagnostic information. In addition, known methods cannot identify the conditions underlying true stroke. A biomarker reflecting neuronal neurotoxicity and the early stage of ischemic dysfunction may provide additional diagnostic data in true stroke. An ideal blood biomarker should be economical, sensitive, specific and reproducible with high

accuracy, has negative and positive predictive value and must be interpreted readily by clinicians [3,13]. In recent years, there has been growing interest in developing biomarkers to determine etiology and stroke type to distinguish conditions mimicking stroke. A panel including NR-2, S100 B, VWF, MMP9, VCAM or S100B or VWF, MMP9, BDNF and MCP-1 can discriminate stroke from controls with high sensitivity and specificity [14]. In a systematic review on blood biomarkers in the diagnosis of ischemic stroke, the authors found important limitations in the design and reporting of all studies despite high sensitivity or specificity [5]. In a recent update, the authors concluded that there is no sufficient evidence that novel biomarkers can distinguish stroke from other causes [15].

In a multicenter study involving 1146 stroke patients, blood samples were analyzed for MMP9, BNP, D-dimer and protein S100. The authors reported that levels of these proteins were the sensitive biomarker for acute stroke [16]. In our study, the NR-2 level was significantly more sensitive for patients with acute stroke when compared to controls, concurring with the above-mentioned study.

Several studies were conducted to distinguish between ischemic stroke and intracerebral hemorrhage. The studies investigated whether several markers have a basal cut-off value for discrimination of these entities, and such a basal cut-off value was defined for some biomarkers such as GFAP [16,17]. In our study, no cut-off value was determined. This finding may be due to differences in genetics, disease severity and blood sampling.

In a recent meta-analysis, activated protein C-protein C inhibitor complex (AOC-PCI), glial fibrillary acidic protein (GFAP), APC-PCI plus GFAP and retinol-binding protein (RBP)-4 levels were evaluated for discrimination of two stroke types. The authors concluded that the results indicate insufficient reliability for routine clinical use [18]. In our study, no meaningful result could be obtained for using the NR-2 peptide level as a prognostic marker despite higher levels of NR-2 peptide in patients with stroke. Another study observed that vascular endothelial growth factor was associated with outcomes on month three and stroke severity [19]. In the early ischemia phase, thrombin-activated serine proteases are activated, and antibody fragments, namely NR-2 peptides, against NMDA are released into the circulation [20]. Antibodies against NMDA receptor peptides (NR-2Abs) develop in response to the release of NR peptide fragments and can be measured in the blood [15]. Studies of NR-2 peptides (degradation products of NMDA NR-2 receptors) have supported NR-2 peptide use as a biomarker in diagnosing stroke. The level of NR-2 peptide is increased following a stroke. IgG antibodies are defined against NMDA receptor fragments, which can be detected in the blood and represent a potential biomarker [8,9]. However, NMDA-R antibodies are also linked to hypertension, atherosclerosis, previous stroke, epilepsy and encephalitis; thus, their specificity is unknown. In our study, the NR-2 level could have been affected by undefined risk factors. However, all known risk factors that may affect NR-2 levels were excluded, resulting in an alteration in the specificity and prognostic value of the antibody.

In a recent study, the authors assessed the value of lipoprotein-associated phospholipase A2 (Lp-PLA2) protein level as a biomarker for diagnosis and prognosis in clinical use; they found a correlation with poor prognoses [21]. Chen et al. [22] evaluated neutrophil, lymphocyte and platelet: lymphocyte ratios in the prognosis of acute stroke. In another study, the authors studied the association between eosinophil: monocyte as biomarker and prognosis in acute ischemic stroke, reporting the ratio as a potential biomarker for prognosis [23]. Yang et al. [24] investigated the relationship between baseline serum complement levels and prognosis, reporting that elevated serum C3 complement levels at diagnosis are associated with poor prognosis. Another study evaluated the relationship of retinoic acid levels with prognosis, reporting that low serum retinoic acid was associated with poor prognosis [25].

Although our study is the first to assess the association between NR-2 levels and prognosis, no such association was found contrary to the relationship between different biomarkers and prognosis. This result may be due to the plasma availability of these two biomarkers studied and

the clinical variation and differences in the cohort.

Although our data shed light on the use of the NR-2 peptide level as a biomarker in the acute phase in patients with stroke, the data is insufficient to predict prognosis. We think that larger, multicenter studies with longer follow-up periods are needed.

CONCLUSION

In conclusion, the NR-2 peptide level is a potential biomarker for further study and validation in patients with acute strokes. However, no correlation was detected with the coma scores. More studies are needed to identify novel biomarkers or biomarker combinations with better discrimination ability for use in diagnosis.

Limitations of study: This study had limitations, including a single-center design, a shorter study period and a smaller sample size. In addition, there may be differences in the time from symptom onset to presentation due to variations in access to emergency medical services, all of which may affect the NR-2 peptide level. The NR-2 peptide is a candidate for use as a biomarker in diagnosing acute stroke in the absence of such limitations.

Conflict of Interest: The authors declare no conflict of interest related to this article.

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ORCID and Author contribution: A**T (0000-0002-3889-819X):** Investigation, Formal analysis, Writing - original draft, Methodology, Formal analysis, Writing - review & editing. **KK (0000-0001-9758-0803):** Conceptualization, Methodology. **FMY (0000-0002-4107-5389):** Formal analysis, Validation, Writing - review & editing. B**C (0000-0002-3308-5843):** Supervision, Writing - review & editing.

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