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ORIGINAL ARTICLE

Can Syndecan-1 Be Used As A Biomarker In Alzheimer's Disease?

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ABSTRACT

Background: Syndecan-1 (SDC-1) is a member of the syndecan family, which includes heparan sulfate proteoglycans. SDC-1 is important for cell-cell and cell-matrix interactions. The aim of this study is to examine the relationship between serum SDC-1 levels and mild cognitive impairment (MCI) and Alzheimer's disease (AD).

Methods: Eighty-two patients aged 65 years and over were included in the study. The Mini-Mental State Examination (MMSE) was used to evaluate the cognitive functions of the patients. Comprehensive geriatric assessment components were administered to the patients. Serum SDC-1 levels were measured with an enzyme-linked immunosorbent assay kit.

Results: When patients were grouped as control, MCI and AD, significant decreases were observed in Katz daily living activity ($p<0.001$), Lawton instrumental daily living activity ($p=0.001$), Mini-nutritional assessment ($p=0.001$), MMSE ($p=0.001$) scores. SDC-1 level was 154.88±22.85 in the control group, 157.95±19.45 in the MCI group, and 159.54±14.04 ng/mL in the AD group, and no significant correlation was observed ($p=0.677$). When correlation analyzes were performed with SDC-1, a negative correlation was found with the Yesavage geriatric depression scale score (Spearman rho: -0.223 $p=0.044$).

Conclusion: No correlation was found between SDC-1 level and AD, and it showed a negative correlation with depression. Clarifying the pathogenetic processes more clearly will guide the development of new treatment strategies.

Keywords: Syndecan-1, Mild cognitive impairment, Alzheimer's disease, Yesavage geriatric depression scale

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia and one of the leading causes of morbidity and mortality in the aging population. AD is neuropathologically characterized by senile plaques formed by the deposition of extracellular amyloid β protein (Aβ) and neurofibrillary tangles formed by the deposition of intracellular hyperphosphorylated tau protein [1]. Although the precise role of Aβ in AD is not fully understood, plaque formation from accumulated Aβ is still thought to be a central event in disease development. It has been shown that the accumulation of Aβ resulting from the imbalance between production and clearance has a profound effect on the pathogenesis of AD. Although neuronal loss caused by inflammation and toxic mechanisms caused by senile plaques and neurofibrillary tangles are known as the main pathogenetic mechanism, it has not been clearly determined how this accumulation occurs in the brain and how it causes neuron loss [2,3].

The interaction of heparan sulfate proteoglycans (HSPGs) with Aβ is well known. HSPGs play a role in various pathogenic features of AD, including its localization with amyloid plaques. Binding of Aβ1–42 to HSPGs is mediated by electrostatic interactions between negatively charged heparan sulfate chains and the cationic heparin-binding motif of Aβ1–42. The binding of Aβ1–42 to heparan sulfate chains induces its multimerization, leading to the formation of toxic fibrillar aggregates [4,5].

The word "syndecan" derives from the Greek word "syndein" meaning "to connect", thus reflecting its biological role. Due to their highly sulfated polyanionic glycosaminoglycan (GAG) chains, SDCs interact with numerous extracellular cationic ligands and transmit signals from the extracellular space to the cellular interior, affecting cellular metabolism, transport, and information transfer. Syndecan-1 (SDC-1) is one of four members of the syndecan family. It is a cell surface protein consisting of three structural domains that bind heparin sulfates and chondroitin sulfates, one of which is extracellular. It is involved in the regulation of cell proliferation, migration, and organization of the cytoskeleton. As key regulators of cell signaling and biological functions, SDCs also have important roles in the pathogenesis of various diseases [6].

There is currently no treatment to stop or reverse the progression of AD. Therefore, further studies are needed to understand the etiopathogenesis of AD and to identify possible new pathological pathways or markers. To our knowledge, there is no study examining serum SDC-1 levels in patients with AD and comparing levels between patients with normal cognitive function and those with MCI. The aim of this study is to evaluate the relationship between serum SDC-1 levels and AD.

MATERIALS AND METHODS

Patient characteristics

A total of 124 patients aged 65 years and older who applied to the geriatrics outpatient clinic, with informed consent, were evaluated, after the exclusion criteria, 82 patients (32 with AD, 30 with MCI and 20 without cognitive impairment) were included in the study. Patients with the following diseases were excluded in the study: 1) Patients with inflammatory diseases, 2) With active infection, 3) With a diagnosis of malignancy, 4) With a diagnosis of heart failure, 5) With vascular dementia, Parkinson's dementia, Lewy body dementia, frontotemporal dementia and other neurodegenerative diseases. Petersen's criteria were used for the diagnosis of MCI [7]. After comprehensive geriatric assessment (CGA) and cognitive evaluation, the diagnosis of dementia was made according to NINCDS-ADRDA [8] and DSM-V [9] criteria. Cognitive dysfunction severity was determined using a modified version of the Reisberg functional assessment staging (FAST) scale [10]. For the differential diagnosis of each patient diagnosed with dementia, magnetic resonance imaging was performed before the diagnosis of AD. Other types of dementia were ruled out.

The patient's age, gender, with whom they lived, educational status, smoking and alcohol use, body mass index (BMI), concomitant diseases, incontinence, history of falling, and the number of drugs used were recorded. The type of study was designed as a cross-sectional study.

Comprehensive Geriatric Assessment and Cognitive Assessment

Within the concept of CGA some standardized tools were applied. The Katz Activity of Daily Living Scale (ADL) [11] and the Lawton-Brody Instrumental Activities of Daily Living (IADL) [12] scales were used to evaluate the functional status of the patients. The Yesavage Geriatric Depression Scale (GDS) short form was administered to the patients to screen for depression [13]. For malnutrition risk assessment, patients were evaluated with the Mini Nutritional Assessment short-form (MNA-SF) [14].

The cognitive status assessment of the patients participating in the study was performed by clinical evaluation and anamnesis from the patient and the caregivers. Screening instruments including Folstein Mini-Mental State Examination (MMSE), and the clock drawing test [15,16]. After the evaluation, and using the mentioned criteria, the patients were grouped as normal, MCI and AD.

Syndecan-1 Measurement

Blood samples were taken from the patients and centrifuged at 4,000 g for 10 minutes. All samples were stored at –80 C until testing. Serum SDC-1 levels were analyzed by enzyme-linked immunosorbent assay (ELISA) using a commercial kit (Human Syndecan-1 CD138 ELISA Kit, Bioassay Technology Laboratory, China) according to the manufacturer's instructions.

The plate is pre-coated with human SDC-1 antibody. SDC-1 present in the sample is added and binds to antibodies coated on the cavities. Biotinylated human SDC-1 antibody is then added and binds to SDC-1 in the sample. Streptavidin-HRP is then added and binds to the Biotinylated SDC-1 antibody. After incubation, unbound Streptavidin-HRP is washed off during a wash step. The substrate solution is then added and color develops in proportion to the amount of human SDC-1. The reaction is terminated by the addition of the acidic stop solution and the absorbance is measured at 450 nm.

Ethics

The study protocol was evaluated and approved by the Hacettepe University Ethics Committee (Ethics committee approval number: GO 17/963). Informed consent was obtained from all the patients.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 22.0. Descriptive statistics were examined using visual (histograms and probability graphs) and analytical methods (Kolmogorov-Smirnov/ Shapiro-Wilk tests) for numerical variables to fit the normal distribution. Descriptive statistics were given using the mean and standard deviation (mean±SD) values for the normally distributed variables, and the median and minimum-maximum values for the non-normally distributed variables. Categorical variables were expressed as numbers and percentages (%). Stundent's t-test and Mann-Whitney U test were used when comparing numerical parameters with normal and non-normal distribution between two independent groups. The Kruskal Wallis test was used when comparing numerical variables that did not show normal distribution with more than two independent groups. One-way Anova test was used to compare the normally distributed numerical parameters with more than two independent groups. The homogeneity of variances was determined using Levene's test. Post-hoc analysis was performed with the TUKEY test when there was significance between the groups. Pearson's test was used for the correlation of normally distributed numerical parameters, and Spearman's test was used for the correlation of abnormally distributed numerical parameters. Chi-square test was performed while analyzing two or more categorical variables. When significance was detected in the Chi-square test in the analysis of more than two categorical variables, post-hoc analysis was performed to determine where the significance originated, and Bonferroni correction was applied to determine the p-value. 'Considering the type 1 error as 0.05 and power as 0.80 in the study, the minimum number of patients included in the study was calculated as 73.'

RESULTS

Out of 82 patients who participated in the study, 44 (53.7%) were female. The mean age was 76.79±6.41 years. 14 patients (17.1%) were university graduates. The most common comorbidities were hypertension (61%), incontinence (40.2%) and diabetes mellitus (29.3%). When grouped as control, MCI, and AD, a significant decrease was observed in the Katz ADL (p<0.001), Lawton IADL (p0.001), MNA-sf (p0.001), MMSE (p0.001) scores. SDC-1 levels were 154.88±22.85 in the control group, 157.95±19.45 in the MCI group, and 159.54±14.04 ng/mL in the AD group. Although there was an increase in SDC-1 level from the control group to the AD group among the groups, no significance was observed (p=0.677). It is shown in detail in Table 1. A box plot graph showing the distribution of serum SDC-1 levels of the patient groups is presented in Figure 1.

When correlation analyzes were performed with SDC-1, a negative correlation was found with Yesavage GDS (Spearman rho: -0.223 p=0.044). No significant correlation was observed with age, ADL, IADL, MMSE score, MNA-SF score (Table 2). When the patients were evaluated according to the Yesavage GDS and grouped as below 5 points and above, the SDC-1 level was 150.543±15.79 ng/mL in depressed patients, and 159.863±18.61 ng/mL in non-depressed patients, and it was significant (p=0.042).

Table 1. Demographic characteristics and clinical data of patients

	Total (n:82)	Control (n:20)	MCI (n:30)	AD (n:32)	p
Female gender, n (%)	44 (53.7)	9 (20.5%)	17 (38.6%)	18 (40.9)	0.671
Age, year	76.79±6.41	72.15±5.38	76.93±6.24	79.56±5.61	**0.017**
Educational level, university graduate, n (%)	14 (17.1)	5 (35.7)	4 (28.6)	5 (35.7)	0.032
Diabetes mellitus, n (%)	24 (29.3)	7 (29.2)	8 (33)	9 (37.5)	0.804
Hypertension, n (%)	50 (61)	13 (26)	20 (40)	17 (34.0)	0.503
Coronary artery disease, n (%)	19 (23.2)	3 (15.7)	7 (36.8)	9 (47.4)	0.551
Incontinence, n (%)	33 (40.2)	6 (18.2)	7 (21.2)	20 (60.6)	**0.004**
Syndecan-1 level, ng/mL	157.81±18.35	154.88±22.85	157.95±19.45	159.54±14.04	0.677
Katz ADL score (min-max)	6 (0-6)	6 (5-6)	6 (5-6)	4 (0-6)	**<0.001**
Lawton-Brody IADL score (min-max)	8 (1-8)	8 (6-8)	8 (4-8)	4 (1-8)	**<0.001**
MNA-SF score (min-max)	13 (1-14)	14 (12-14)	14 (10-14)	11 (1-14)	**<0.001**
Yesavage GDS score (min-max)	2 (0-10)	2 (0-10)	2 (0-10)	2 (0-9)	0.582
MMSE score (min-max)	26 (3-30)	30 (25-30)	27 (18-30)	20 (3-29)	**<0.001**

* SD, standard deviation; MMSE, Mini-Mental State Examination; ADL, Katz Activity of Daily Living; IADL, Lawton Instrumental Activities of Daily Living; MNA-SF, short-form Mini-Nutritional Assessment; GDS, Geriatric Depression Scale.

Table 2. Correlation analysis results of Syndecan-1

	Syndecan-1 level and the correlation coefficient	p
Age	0.05	0.66
ADL	0.096	0.40
IADL	0.035	0.754
MMSE score	0.072	0.521
MNA-SF score	-0.032	0.773
Yesavage GDS score	-0.223	**0.044**

* ADL: Activities of Daily Living, IADL: Instrumental Activities of Daily Living, MMSE: Mini-Mental State Examination, MNA-sf: Mini Nutritional Assessment short-form, GDS: Geriatric Depression Scale.

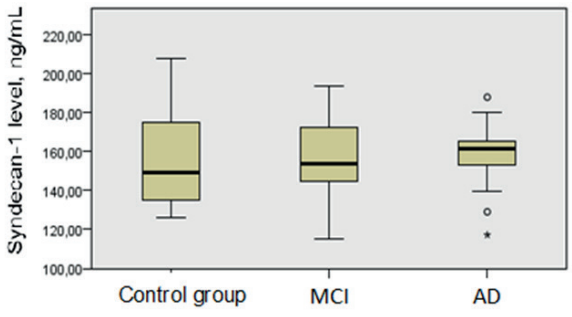

Figure 1. Box plot graph showing the distribution of serum syndecan-1 levels of the patient groups. Values of serum syndecan-1 levels were 154.88±22.85, 157.95±19.45, and 159.54±14.04 ng/mL for the control, MCI, and AD groups, respectively (0.677). MCI: mild cognitive impairment, AD: Alzheimer disease.

DISCUSSION

In this study, the relationship between serum SDC-1 levels and AD were investigated. SDC-1 levels were not different between patients with normal cognitive function, MCI, and AD. While a significant correlation was observed between serum SDC-1 level and Yesavage GDS score, no significant correlation was found with MMSE scores. To our knowledge, this is the first study to analyze serum SDC-1 levels in patients with AD, MCI and normal cognitive function. Although SDC-1 levels had a tendency to increase with cognitive dysfunction, this result was not statistically significant. Therefore, SDC-1 failed to be used as a potential biomarker for AD.

SDCs are the transmembrane HSPG family. SDCs contain a short cytoplasmic domain, a transmembrane domain, and an extracellular domain with additional binding sites for three to five heparan sulfate (HS) or chondroitin sulfate (CS) chains. The HS chains of SDCs enable interaction with many extracellular ligands, while their cytoplasmic domains facilitate intracellular signaling cascades [17]. Among SDCs, SDC-1 has been previously reported to increase cellular uptake of ApoE-containing lipoproteins, thereby facilitating hepatic lipoprotein clearance. Besides the liver, it shows the highest expression of ApoE in the central nervous system. ApoE is also associated with AD according to its isoform in the brain. ApoE2 reduces the risk of AD, while ApoE4 increases it 4 to 14 times [18]. It has been suggested that ApoE is involved in the plaque formation mechanism by directly interacting with amyloid-beta (Aβ) or reducing Aβ clearance [19]. A recent study has presented findings supporting the interaction of ApoEs with HSPGs and the effects of ApoEs on Aβ1-42 uptake and aggregation. On the other hand, it has provided new insights into the molecular interaction of ApoEs with SDCs, a family of transmembrane proteoglycans whose importance is emerging in the pathomechanism of neurodegeneration. In this study, since SDC-3 plays a dominant role in the SDC family, the weak effect of SDC-1 in these mechanisms was also mentioned [20]. In our study, although the SDC-1 level showed an increasing trend from normal cognitive function to AD, no significant relationship was found. This may be attributed to the small number of patients included in the study.

As blood is more accessible than CSF, measuring AD biomarkers is preferred when it comes to sampling for diagnosis and screening. However, developing blood biomarkers for AD has been proven difficult. While CSF is continuous with brain extracellular fluid by free molecule exchange from the brain to CSF, only a part of brain proteins enters blood circulation. Brain proteins released into the blood can be broken down by proteases, metabolized in the liver, or cleared by the kidneys, resulting in a difficult-to-measure condition. For these reasons, the potential to find blood biomarkers for AD is limited [21]. Nevertheless, technical advances in ultrasensitive immunoassays and mass spectrometry have brought new hopes for biomarker discovery [22].

Although amyloid plaques have been defined as primary pathological lesions in AD, studies are still ongoing on how these plaques form in the brain. Increasing evidence suggests that angiogenic vascular factors may play a role in the pathogenic mechanism of AD [23]. Heparan sulfate proteoglycan SDC-1 modulates cell proliferation, adhesion, migration, and angiogenesis. Many studies have shown that SDC-1 may be associated with a number of diseases [6]. The mechanism that could explain the relationship between serum SDC-1 levels and depression is unknown. As a possible mechanism, cortisol levels increase in depression. It is known that depression in advanced age is associated with increased activity of the hypothalamic-pituitary-adrenal (HPA) axis [24]. Considering the studies on SDC-1 and cortisol, it was seen that cortisol suppressed the SDC-1 concentration [25]. In the light of these studies, it is suggested that serum levels may be low in the depression group due to the inhibitory effect of high cortisol on SDC-1 production. In our study, a negative correlation was found between SDC-1 and Yesavage GDS. When the patients were evaluated according to the Yesavage GDS and grouped as below 5 points and above, the SDC-1 level was found to be significantly lower in the patients who scored 6 points and above. There is no article in the literature examining the relationship between SDC-1 and depression.

This study has several limitations. The study was designed as cross-sectional and it has a small sample size. It is thought that the SDC-1 level, which gradually increased from the control group to the AH group, did not create significance due to the small sample size.

It is thought that future therapeutics should be applied in the preclinical and MCI stages of the AD course to maintain the current status. Clarifying the pathogenetic processes more clearly will guide the development of new treatment strategies. This study is important for studying a novel factor as a possible pathogenetic mechanism. However, probably due to small sample size it failed to prove the hypothesis. More extensive studies are needed on this subject.

Author contribution

Study conception and design: RTD, BBD, MH, and MC; data collection: RTD, CC, GSA, CO, HC, and HDV; analysis and interpretation of results: RTD, CC, HDV, and ZGD; draft manuscript preparation: RTD and BBD. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Ethics Committee (Protocol no. GO 17/963/16.01.2018).

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Conflict of interest

The authors declare that there is no conflict of interest.

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