Acta Neurologica Belgica
https://doi.org/10.1007/s13760-020-01477-1

ORIGINAL ARTICLE

Evaluation of serum galectin-3 levels at Alzheimer patients by stages: a preliminary report

Tamer Yazar[1,2] · **Hülya Olgun Yazar**[3,4] · **Murat Cihan**[4]

Received: 21 April 2020 / Accepted: 17 August 2020

Abstract

Background and Aims Neuroinflammation has a critic role in the pathophysiology of neurological diseases. The activation of microglia is the main actor in this process. The aim of this study to collect data on the role of microglial activation in the etiology, and the possible continuum at the stage of disease through the evaluation of serum galectin-3 levels in patients with Alzheimer's disease (AD).

Methods This was a prospective and cross-sectional study conducted on patients who were diagnosed as having AD using the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) and stages determined with the scales of Clinical Dementia Rating (CDR) and Mini-Mental State Examination (MMSE) with healthy controls.

Results In our study, we studied 118 people, 57 with AD and 61 healthy people as a control group. In the AD patient group, serum galectin-3 levels were higher compared with the control group ($p = 0.003$). There were no significant differences in either group in other collected parameters ($p > 0.05$). It was observed that in all patients with AD, parallel to the stage of the disease, serum galectin-3 levels, patience's age, and duration of disease were statically and significantly increased ($p < 0.05$).

Conclusion In conclusion, serum galactin-3 levels may be associated with AD and maybe a potential biomarker for the identification of disease in the early stages. In future years, serum galectin-3 levels may become an important biomarker and therapeutic agent for chronic neurodegenerative diseases such as AD.

Keywords Alzheimer's disease · Disease severity · Galactin-3 · Microglial activation · Neurodegeneration · Neuroinflammation

Introduction

Dementia is a major health problem whose prevalence increases with age. Alzheimer's disease (AD) is the most frequently seen among all dementia types. This process of neurodegenerative disease is classically characterized by two distinct pathologies: hyperphosphorylated tau neurofibrillary tangles and aggregations of β-amyloid plaques. The main etiologic and pathophysiologic mechanisms that create AD are oxidative stress, inflammation, and mitochondrial dysfunction [1–6].

Neuroinflammation has a critic role in the pathophysiology of acute and chronic neurologic disease. The connection between neurodegenerative diseases and neuroinflammation has been shown in clinical and experimental studies [7–10]. The activation of microglia is the main actor in this process. Microglial cells are macrophages of the central nervous system (CNS) and are responsible for the innate immune

✉ Tamer Yazar
tamer.yazar@yahoo.com.tr

Hülya Olgun Yazar
hulyazar@yahoo.com

Murat Cihan
mcihan@gmail.com

1 Neurology, Ordu State Hospital, Dr. Fahrettin Önsel Cd., Altınordu, PK:52200 Ordu, Turkey

2 Zeytinburnu Surp Pirgıç Armenian Hospital, İstanbul, Turkey

3 Taksim Training and Research Hospital, İstanbul, Turkey

4 Neurology, Ordu University Training and Research Hospital, Ordu, Turkey

Published online: 27 August 2020

response. They show dual effects of modulating neuroinflammation and cell death [8, 11–13]. Microglial cells have different functions, so activation of microglial cells is essential for proper function in the diseased and healthy brain. Chronic activation of microglial cells creates a proinflammatory environment that is important for the development and progress of the disease. This environment caused by the chronic activation of microglial cells and microglial activity is considered to be decisive in the pathogenesis of AD due to protein aggregation [12–18].

Galectin-3 is a member of the galectin family including β galactoside lectins, which are produced or secreted by eosinophils, macrophages, mast cells, and various tissues. Galectin-3 is an immune-modulating agent that has a role in different biologic activities such as cell proliferation, activation, adhesion, macrophage activation, phagocytosis, migration, angiogenesis, and apoptosis [10]. Also, galectin-3 acts as an endogenous ligand for TLR4 driving microglial activation [20]. Increasing levels of galectin-3 are associated with various diseases including autoimmune diseases, cancers, cardiovascular diseases, and neurodegenerative diseases [10, 19–22]. Previous studies have reported an increase at Galectin-3 levels in microglia [19, 23]. In a study by Jang et al. in 2009, in an experimental autoimmune encephalomyelitis, Galectin-3 deficiency was reported to reduce disease severity and inflammation [24]. In another study, galectin-3 deficiency has been shown to increase ischemic damage after cerebral ischemia [23]. Siew et al. stated in their study in 2019 that Galectin-3 is required for microglia-related inflammation in Huntington disease [25]. These studies show us that galectin-3 has a completely unexplained role in microglial inflammation.

Microglial activation is associated with many neurodegenerative diseases [3, 4, 17, 26–28]. As a result, pharmacologic interventions for inflammation that develops due to microglial activation may be a hopeful therapeutic target. In our study, it was aimed to collect data on the role of the microglial activation/inflammation in the etiology of AD, and the possible effects on the continuum of the stages of the disease through the detection of serum galectin-3 levels in patients with AD by disease stage.

Materials and methods

Population and sample

Our study was performed on 118 people, 57 who were diagnosed as having AD according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria and staged using the scales of the Clinical Dementia Rating (CDR) and Mini-Mental State Examination (MMSE), and 61 healthy people with the same age, sex, and body mass index (BMI) [29].

For the patient and control groups, chronic diseases except for regulated hypertension, an acute or chronic infectious condition, malnutrition, obesity, cigarette or alcohol use, and using medication that could affect the neuroinflammatory system (e.g. steroids, immunosuppressive) were considered as exclusion criteria.

Data collection tools

For both the patient and control groups, every individual's chronic diseases, a medicine used, and BMI were recorded. The MMSE was conducted for both the patient and control groups, and CDR staging was only performed for the AD patient group.

The CDR is used to determine functional destruction through the evaluation of memory, orientation, judgement and problem-solving, public events, hobbies, and personal hygiene in patients with AD. Its stages are divided as 0 (no destruction) to 3 (severe dementia) [5, 30].

The MMSE is a standardized test that is used to evaluate the mental level under five main topics, which are orientation, record memory, attention, calculation, remembering, and language. The Turkish validity and reliability studies have been completed [31].

Analysis of biochemical parameters

Venous blood samples were taken from patients and healthy controls after 12–14 h' fasting. Separator gel tubes were used to obtain serum, with potassium-EDTA tubes used for blood counts. After being centrifuged for 10 min at 3000 rpm, plasma was separated and stored at − 80 °C. Serum C-reactive protein (CRP) levels were studied in our laboratory. CRP values were analyzed by wr-CRP and method on a Cobas c501 analyzer, using the latex-enhanced immunoturbidimetric assay (wr-CRP: C-Reactive protein Gen. 3 reagent kit, turbidity measurement at 546 nm; the analytic measurement range of wr-CRP and was 0.3–350 mg/L. Complete blood count (CBC) were collected from the results. Galectin-3 levels in human blood are evaluated using an enzyme-linked immunosorbent assay (ELISA) kit. The plate has been precoated with human GALECTIN-3 antibody. GALECTIN-3 present in the sample is added and binds to antibodies coated on the wells. And then biotinylated human GALECTIN-3 Antibody is added and binds to GALECTIN-3 in the sample. Then Streptavidin-HRP is added and binds to the Biotinylated GALECTIN-3 antibody. After incubation unbound Streptavidin-HRP is washed away during a washing step. Substrate solution is then added and color develops in proportion to the amount of human GALECTIN-3. The reaction is terminated by addition of acidic stop solution and

absorbance is measured at 450 nm. Galectin-3 levels are calculated as pg/dL.

Statistical analysis

Statistical analysis of data was performed using SPSS 22.0; Analyze- it and Medcalc stastical programs. Demographic data are summarized as number, mean and standard deviation. To test for normal distribution of data, the Kolmogorov–Smirnov test was used for samples larger than 50, and the Shapiro–Wilk test was used for smaller samples. The comparison of categoric variables was performed using Fisher's exact test. For the comparison of two groups of numerical values, the Mann–Whitney U test was used for samples without normal distribution, and the independent samples *t* test was used for samples with a normal distribution. Mann–Whitney U test was used to compare numerical values in three groups for samples without normal distribution and one-way analysis of variance (ANOVA) for samples with a normal distribution. After multiple comparisons, to assess which group(s) caused the differences, Bonferroni comparison test used. Spearman's rho correlation test was used to compare samples with continuous variables. All tests took the statistical significance level as $p < 0.05$.

Results

In the study, we analyzed 118 people, 57 with AD and 61 healthy people as a control group. The serum galectin-3 levels were significantly higher in patients with AD compared with the control group ($p = 0.003$). There were no significant differences between the patients with AD and controls in any of the other collected parameters ($p > 0.05$) (Table 1).

It was observed that in all patients with AD, parallel to the stage of the disease, serum galectin-3 levels, patience's age, and duration of disease were statically and significantly increased ($p < 0.05$). In addition, MMSE scores significant decreased with increasing disease stage in both sexes ($p < 0.05$) (Table 2, Fig. 1).

Table 1 Demographic, anthropometric, and blood parameters in the Alzheimer and control groups

Trait	AH		Control		*p*-value
	n	Mean ± SD	*n*	Mean ± SD	
Age (years)	57	79.05 ± 6.96	61	77.65 ± 7.665	0.257
Sex	57		61		0.410
Female	35		37		
Male	22		24		
MMSE	57	17.86 ± 4.295	61	28.02 ± 1.157	***< 0.001***
BMI (kg/m^2)	57	26.725 ± 3.053	61	26.484 ± 2.28	0.214
Hemoglobin (g/dL)	57	13.902 ± 0.898	61	13.797 ± 1.252	0.547
CRP (mg/dL)	57	0.113 ± 0.066	61	0.145 ± 0.098	0.308
Neutrophil (K/μL)	57	3.527 ± 0.848	61	4.013 ± 1.223	0.058
Urea (mg/dL)	57	31.528 ± 7.612	61	28.665 ± 6.967	0.053
Creatinine (mg/dl)	57	0.782 ± 0.082	61	0.762 ± 0.091	0.220
Galectin-3 (pg/ml)	57	238.524 ± 160.17	61	178.001 ± 8.329	0.003

Mean ± standard deviation, Statistical significance level $p < 0.05$, CRP: C-Reactive Protein, BMI: Body Mass Index, MMSE: Mini Mental State Examination

Discussion

It has been reported in different studies that in neurodegenerative diseases, mainly AD and Parkinson's disease (IPH), and in many neurologic conditions such as trauma or ischemic brain damage, encephalomyelitis, epilepsy, mediated neuroinflammation, increased plasma galectin-3 levels via the peripheral immune system and glia are important in the etiopathogenesis [10, 13, 32–37]. Studies have found that Galectin -3 acts as a biomarker for diagnosis or prognosis of many systemic diseases and cancers [35, 37–39]. The inflammatory hypothesis of AD tries to explain the progression of the disease from the point of view of the activation of the innate immune system in the brain. One of the main actors in this hypothesis is microglial cells. The main components of the innate immune system in the CNS are microglial cells, astrocytes, oligodendrocytes, neutrophils, and the complement system. Microglia are homologues of macrophages in the CNS and they share similar functions, such as debris clearance, neural development, phagocytosis of apoptotic cells, and synaptic formation [35, 36, 40, 41].

Galectin-3 is a very useful protein that creates a proinflammatory reaction by activating the microglia, lymphocytes, and macrophages, and it is reported to have a close connection in diseases showing neurodegeneration[19, 20, 40, 42]. Galectin-3 is an inflammatory tool that is known to be highly expressed in some activated inflammatory cells including microglia [10, 16]. Ashraf et al. evaluated galectin-3 levels in the brain, spinal cord fluid, and serum samples in 31 patients with AD, 19 with amyotrophic lateral sclerosis (ALS), and 50 healthy people in 2018 and they found galectin-3 levels were significantly higher in the patient groups than in the control group [40]. Similarly, Wang et al. reported that galectin-3 played a role in neuropathogenesis and might be a potential biomarker for AD [43]. Another study found that galectin-3 contributed to the permanent destruction of the blood–brain barrier in secondary

Table 2 Data for male and female patients with AD according to stage

Sex	Stage 1		Stage 2		Stage 3		*p*-value
	n	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	
Females							
Age (years)	19	76.63 ± 6.542	10	82.4 ± 5.016	6	87.83 ± 7.083	0.005
DD (years)	19	2.42 ± 0.961	10	6.5 ± 3.171	6	8 ± 1.897	***< 0.001***
Galectin-3 (pg/mL)	19	168.97 ± 57.152	10	252.285 ± 57.104	6	483.035 ± 362.56	***< 0.001***
MMSE	19	19.89 ± 1.449	10	15.9 ± 3.381	6	10 ± 3.578	***< 0.001***
Males							
Age (years)	13	74.77 ± 5.615	6	80 ± 4.382	3	82.33 ± 3.786	0.040
DD (years)	13	2.62 ± 1.121	6	5 ± 2.757	3	9 ± 1	0.006
Galectin-3 (pg/mL)	13	193.623 ± 100.423	6	211.962 ± 53.256	3	391.83 ± 35.977	0.020
MMSE	13	21.62 ± 1.387	6	17 ± 2.366	3	12.67 ± 3.215	0.001
Total							
Age (years)	32	75.88 ± 6.158	16	81.5 ± 4.789	9	86 ± 6.519	***< 0.001***
DD (years)	32	2.5 ± 1.016	16	5.94 ± 3.021	9	8.33 ± 1.658	***< 0.001***
Galectin-3 (pg/mL)	32	178.985 ± 77.147	16	237.164 ± 57.519	9	452.633 ± 290.79	***< 0.001***
MMSE	32	20.59 ± 1.643	16	16.31 ± 3.005	9	10.89 ± 3.516	<0.001

Mean ± standard deviation, statistical significance level $p < 0.05$, DD: disease duration, MMSE: Mini-Mental State Examination

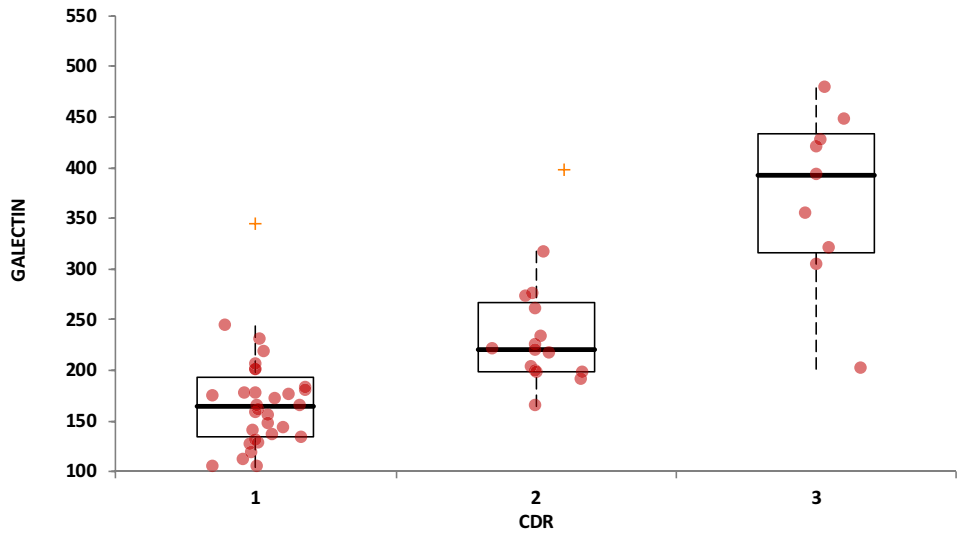

Fig. 1 The relationship between galectin -3 level and stage in patients with AD

progressive multiple sclerosis (SPMS) and suggested it as a new biomarker for SPMS [44]. In another study conducted with 45 IPH patients, serum Galectin-3 levels were significantly higher in the patient group compared to the control group. In the same study, serum Galectin 3 levels were found to be significantly higher in parallel with disease severity and duration[10]. Boza-Serrano et al. found that galectin 3 levels were higher in Alzheimer and rat AD brains. Their study revealed that galectin-3 deficiency improved cognitive behavior by reducing the burden of beta-amyloid plaques in rat' brains [45]. In our study, the role of microglial activation, which is considered to be important in the disease pathogenesis, was evaluated by comparison of disease stage and patient's sex with serum galectin-3 levels in patients with AD. Our data showed that serum galectin-3 levels were higher in patients with AD compared with the control group, in parallel with increasing disease stage.

An important superiority of the study was that there was no statistically significant difference between the patient and control groups in terms of other parameters as age, gender, urea, creatinine, hemoglobin, neutrophil, CRP, BMI levels. Our studies important limitations were our study's cross-sectional design, our sample size being small and the patient and control groups' exercise frequency, and the possible effects of medicines they were using not being evaluated were the important limitations of our study. Accordingly,

further comprehensive studies with larger study population on the relation of AD and serum galectin-3 levels are needed.

Conclusion and recommendations

In conclusion, serum galactin-3 levels may be associated with AD and may be a potential biomarker for the identification of disease in the early stages. In future years, serum galectin-3 level will likely become an important biomarker and therapeutic agent for chronic neurodegenerative diseases such as AD.

Acknowledgments We would like to thank Umut Kağan KELLECİ for his contributions to the article.

Author contributions All authors contributed to writing the manuscript. All authors read and approved the final manuscript. Conceptualization: TY, HOY, Data collection: TY, HOY, MC, Formal analysis: MC, TY, Investigation: TY, HOY, Methodology: TY, HOY, MC, Resources: TY, HOY, MC, Supervision: TY, HOY, Writing—original draft: TY, HOY, MC, Writing—review & editing: HOY, TY.

Funding The funding sponsors had no role in the design of the study, in the collection, analyses, or interpretation of data, in the writing of the manuscript, and in the decision to publish the results.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical aspect of the research and consent to participate To perform the study, permission was granted by Ordu University Education and Research Hospital ethics committee (Decision number: 2019/14). All patients provided written informed consent.

References

1. Peall KJ, Robertson NP (2015) Biomarkers in Alzheimer's disease: understanding disease trajectory and therapeutic targets. J Neurol 262(9):2195–2197. https://doi.org/10.1007/s00415-015-7881-6
2. Daly A, Walsh D (2019) Dementia-a majorpublichealth problem: the role of in-patientpsychiatricfacilities. Iran J Med Sci 188(2):641–647. https://doi.org/10.1007/s11845-018-1858-2
3. Song IU, Chung SW, Kim YD et al (2015) Relationship between the hs-CRP as non-specific biomarker and Alzheimer's disease according to aging process. Int J Med Sci. 12(8):613–617. https://doi.org/10.7150/ijms.12742
4. Alexiou A, Soursou G, Yarla NS et al (2018) Proteins commonly linked to autism spectrum disorder and Alzheimer's disease. Curr Protein Pept Sci 19(9):876–880
5. Yazar T, Yazar HO, Demir EY et al (2018) Assessment of the mental health of carers according to the stage of patients with diagnosis of Alzheimer-type dementia. Neurol Sci 39(5):903–908. https://doi.org/10.1007/s10072-018-3293-6
6. Jung Y, Whitwell JL, Duffy JR et al (2016) Regional β-amyloid burden does not correlate with cognitive or language deficits in Alzheimer's disease presenting as aphasia. Eur J Neurol 23(2):313–319. https://doi.org/10.1111/ene.12761
7. Tiwari PC, Pal R (2017) The potential role of neuroinflammation and transcription factors in Parkinson disease. Dialog Clin Neurosci 19(1):71–80
8. Timmerman R, Burm SM, Bajramovic JJ (2018) An overview of in vitro methods to study microglia. Front Cell Neurosci 12:242. https://doi.org/10.3389/fncel.2018.00242
9. Niranjan R (2018) Recent advances in the mechanisms of neuroinflammation and their roles in neurodegeneration. Neurochem Int 120:13–20. https://doi.org/10.1016/j.neuint.2018.07.003
10. Yazar HO, Yazar T, Cihan M (2019) A preliminary data: evaluation of serum Galectin-3 levels in patients with idiopathic Parkinson's disease. J Clin Neurosci 70:164–168. https://doi.org/10.1016/j.jocn.2019.08.032
11. Wu ZS, Lo JJ, Wu SH et al (2018) Early hyperbaric oxygen treatment attenuates burn-induced neuroinflammation by inhibiting the galectin-3-dependent toll-like receptor-4 pathway in a rat model. Int J Mol Sci 19(8):2195. https://doi.org/10.3390/ijms19082195
12. Gomes-Leal W (2019) Why microglia kill neurons after neural disorders? The friendly fire hypothesis. Neural Regen Res 14:1499–1502
13. Schetters STT, Gomez-Nicola D, Garcia-Vallejo JJ et al (2018) Neuroinflammation: microglia and T Cells Get Ready to Tango. Front Immunol 8:1905. https://doi.org/10.3389/fimmu.2017.01905
14. Boza-Serrano A, Reyes JF, Rey NL et al (2014) The role of Galectin-3 in α-synuclein-induced microglial activation. Acta Neuropathol Commun 2:156. https://doi.org/10.1186/s40478-014-0156-0
15. Streit WJ, Mrak RE, Griffin WS (2004) Microglia and neuroinflammation: a pathological perspective. J Neuroinflamm 1(1):14. https://doi.org/10.1186/1742-2094-1-14
16. Boza-Serrano A, Yang Y, Paulus A et al (2018) Innate immune alterations are elicited in microglial cells before plaque deposition in the Alzheimer's disease mouse model 5xFAD. Sci Rep 8(1):1550. https://doi.org/10.1038/s41598-018-19699-y
17. Bazan NG, Halabi A, Ertel M, Petasis NA (2012) Neuroinflammation. Basic Neurochem. https://doi.org/10.1016/b978-0-12-374947-5.00034-1
18. Ross CA, Poirier MA (2004) Protein aggregation and neurodegenerative disease. Nat Med 10:S10–S17
19. Burguillos MA, Svensson M, Schulte T et al (2015) Microglia-secreted galectin-3 acts as a toll-like receptor 4 ligand and contributes to microglial activation. Cell Rep 10(9):1626–1638. https://doi.org/10.1016/j.celrep.2015.02.012
20. Tripathi M, Dixit A (2016) Chandra PS (2016) Galectin-3, an important yet unexplored molecule in drug resistant epilepsy. Neurol India 64:237–238
21. Shin T (2013) The pleiotropic effects of galectin-3 in neuroinflammation: a review. Acta Histochem 115:407–411. https://doi.org/10.1016/j.acthis.2012.11.010
22. de Boer RA, van Veldhuisen DJ, Gansevoort RT et al (2012) The fibrosis marker galectin-3 and outcome in the general population. J Intern Med 272(1):55–64. https://doi.org/10.1111/j.1365-2796.2011.02476.x
23. Lalancette-Hébert M, Swarup V, Beaulieu JM et al (2012) Galectin-3 is required for resident microglia activation and proliferation in response to ischemic injury. J Neurosci 32(30):10383–10395. https://doi.org/10.1523/jneurosci.1498-12.2012
24. Jiang HR, Al Rasebi Z, Mensah-Brown E, Shahin A, Xu D, Goodyear CS, Fukada SY et al (2009) Galectin-3 deficiency reduces the severity of experimental autoimmune encephalomyelitis. J Immunol 182(2):1167–1173

25. Siew JJ, Chen HM, Chen HY et al (2019) Galectin-3 is required for the microglia-mediated brain inflammation in a model of Huntington's disease. Nat Commun 10(1):3473. https://doi.org/10.1038/s41467-019-11441-0
26. Di Sabato DJ, Quan N, Godbout JP (2016) Neuroinflammation: the devil is in the details. J Neurochem 139(Suppl 2):136–153. https://doi.org/10.1111/jnc.13607
27. Norden DM, Godbout JP (2013) Review: microglia of the aged brain: primed to be activated and resistant to regulation. Neuropathol Appl Neurobiol 39:19–34
28. Schwartz M, Kipnis J, Rivest S et al (2013) How do immune cells support and shape the brain in health, disease, and aging? J Neurosci 33:17587–17596. https://doi.org/10.1523/jneurosci.3241-13.2013
29. McKhann G, Drachman D, Folstein M et al (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 34(7):939–944
30. Yazar T, Yazar HO (2019) Assessment of serum uric acid levels according to sex and stage for patients with alzheimer-type dementia. Turk J Neurol 25(2):76–81. https://doi.org/10.4274/tnf.galenos.2019.85698
31. Olgun Yazar H, Yazar T (2019) Prevalence of sarcopenia in patients with geriatric depression diagnosis. Iran J Med Sci 188(3):931–938. https://doi.org/10.1007/s11845-018-01957-7
32. Jiang HR, Al Rasebi Z, Mensah-Brown E et al (2009) Galectin-3 deficiency reduces the severity of experimental autoimmune encephalomyelitis. J Immunol 182:1167–1173. https://doi.org/10.4049/jimmunol.182.2.1167
33. Pajoohesh-Ganji A, Knoblach SM, Faden AI et al (2012) Characterization of inflammatory gene expression and galectin-3 function after spinal cord injury in mice. Brain Res 1475:96–105. https://doi.org/10.1016/j.brainres.2012.07.058
34. Brockmann K, Schulte C, Schneiderhan-Marra N et al (2017) Inflammatory profile discriminates clinical subtypes in LRRK2-associated Parkinson's disease. Eur J Neurol 24(2):427. https://doi.org/10.1111/ene.13223
35. Venkatraman A, Hardas S, Patel N et al (2018) Galectin-3: an emerging biomarker in stroke and cerebrovascular diseases. Eur J Neurol 25(2):238–246. https://doi.org/10.1111/ene.13496
36. Arora P, Agarwal Z, Venkatraman A et al (2017) Galectin-3 and risk of ischaemic stroke: reasons for geographic and racial differences in stroke cohort. Eur J Neurol 24(12):1464–1470. https://doi.org/10.1111/ene.13440
37. Nishikawa H, Suzuki H (2018) Possible Role of Inflammation and galectin-3 in brain injury after subarachnoid hemorrhage. Brain Sci 8(2):30. https://doi.org/10.3390/brainsci8020030
38. Dong R, Zhang M, Hu Q, Zheng S, Soh A, Zheng Y et al (2018) Galectin-3 as a novel biomarker for disease diagnosis and a target for therapy (Review). Int J Mol Med 41(2):599–614. https://doi.org/10.3892/ijmm.2017.3311
39. Sciacchitano S, Lavra L, Morgante A, Ulivieri A, Magi F, De Francesco G et al (2018) Galectin- 3: one molecule for an alphabet of diseases, from A to Z. Int J Mol Sci 19(2):E379. https://doi.org/10.3390/ijms19020379
40. Ashraf GM, Baeesa SS (2018) Investigation of Gal-3 expression pattern in serum and cerebrospinal fluid of patients suffering from neurodegenerative disorders. Front Neurosci 12:430. https://doi.org/10.3389/fnins.2018.00430
41. Ransohoff RM, Schafer D, Vincent A et al (2015) Neuroinflammation: ways in which the immune system affects the brain. Neurotherapeutics 12(4):896–909. https://doi.org/10.1007/s13311-015-0385-3
42. Ma Z, Han Q, Wang X, Ai Z et al (2016) Galectin-3 inhibition is associated with neuropathic pain attenuation after peripheral nerve injury. PLoS ONE 11(2):e0148792. https://doi.org/10.1371/journal.pone.0148792
43. Wang X, Zhang S, Lin F et al (2015) Elevated galectin-3 levels in the serum of patients with Alzheimer's disease. Am J Alzheimers Dis Other Demen 30(8):729–732. https://doi.org/10.1177/1533317513495107
44. Nishihara H, Shimizu F, Kitagawa T et al (2017) Identification of galectin-3 as a possible antibody target for secondary progressive multiple sclerosis. Mult Scler J 23(3):382–394. https://doi.org/10.1177/1352458516655217
45. Boza-Serrano A, Ruiz R, Sanchez-Varo R et al (2019) Galectin-3, a novel endogenous TREM2 ligand, detrimentally regulates inflammatory response in Alzheimer's disease. Acta Neuropathol 138(2):251–273. https://doi.org/10.1007/s00401-01