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Original Article

Assessment of serum galectin-3 levels in acute rheumatic fever

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ABSTRACT

Background. Galectin-3 is a biomarker which takes a role in both acute and chronic inflammation as well as fibrosis and oxidative stress. Increased levels of it are associated with cardiovascular diseases. This study was performed to investigate the levels of galectin-3 in acute rheumatic fever (ARF).

Methods. 30 patients with ARF and 26 healthy children were included. Galectin-3 levels of the patients were compared with the controls, as well as within the patients before and after the treatment.

Results. The patients had significantly lower galectin-3 levels on admission than the control (p=0.02), but its levels were not significantly different between these groups at the end of treatment (p=0.714). The mean galectin-3 levels of the patients were increased after the treatment (p<0.001). Severity of carditis and galectin-3 levels were negatively correlated (r=-539, p=0.02).

Conclusions. Children with ARF have significantly reduced levels of galectin-3 and there is a negative correlation between the severity of the carditis and galectin-3 levels. Studies with larger sample sizes may give more accurate data about the role of galectin-3 in ARF.

Key words: galectin-3, acute rheumatic fever, children.

Acute rheumatic fever (ARF) is still an epidemic in developing countries.[1,2] Globally 471000 cases of ARF are diagnosed annually and deaths that occur due to ARF or rheumatic heart disease (RHD) are still not uncommon, especially in non-developed or developing countries.[3] Two separate pathways for diagnosis have been defined for low and moderate/high-risk populations in revised Jones Criteria, in 2015.[2] Joints and the heart are most commonly involved.[4]

Galectin-3 is a multifunctional β-galactosidase-binding lectin and plays a role in apoptosis and cell proliferation.[5,6] It plays a role in oxidative stress, inflammation and fibrosis.[7] It may mediate processes during inflammation including activation of mast cells, neutrophil activation and adhesion, chemotaxis and opsonization of apoptotic neutrophils.[8] Galectin-3 levels have been extensively studied in various viral infections and diseases affecting ophthalmological, renal, cardiovascular, and neurological systems.[9-13] Galectin-3 is reported to be associated with increased risk of heart failure, arrhythmias, atherosclerosis, and an indicator of the severity of heart diseases.[14] It was also proposed to be associated with poor prognosis in acute heart failure.[15]

We aimed to evaluate the role of galectin-3 in children with ARF.

Material and Methods

The study was carried out between October 2018 and October 2019. Informed constant was

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obtained from all. The study was approved by ethics committee of Van Training and Research Hospital (Approval date and number: 04.10.2018 - 2018/14).

The galectin-3 levels were compared between patients and the controls on admission and after the treatment. Also, the correlation between severity of carditis and galectin-3 levels was analyzed.

Study population

Thirty patients with ARF as study group and 26 children as control group were included. The study group was also subdivided based on the degree of carditis. Children with a history of any other diseases or any medication were not included.

History taking, physical examination, diagnosis, and management

All participants were asked to provide demographic information as well as a comprehensive history. A thorough physical assessment was conducted. Electrocardiography and echocardiography were performed for all individuals. The Jones Criteria, which were modified in 2015, were used to make the diagnosis of ARF.[2] All the patients were hospitalized at least for two weeks. The carditis was classified according to its severity in the light of report of Cannon et al.[16]

Benzathine penicillin G was used for the treatment of pharyngitis and for secondary prophylaxis.[4] Oral prednisolone was used in cases with severe or moderate carditis otherwise, naproxen sodium was used.[17] Appropriate treatment for heart failure and bed rest with activity restriction was decided.

Cardiac evaluation

A detailed echocardiographic evaluation of all participants was performed with a Vivid 7 Pro echocardiography device (GE Vingmed, Horten, Norway). Rheumatic valvulitis was diagnosed using the 2015 Revised Jones Criteria.[2]

Laboratory work-up

Galectin-3 levels and routine laboratory tests were assessed on admission and after treatment. The control group's galectin-3 levels were also tested. Each blood sample collected for galectin-3 analysis were coded by a nurse to have a blinded study. The blood samples were clotted for 2 hours on room air and centrifuged at 1000 × g at 2-8°C for 15 minutes. The serum was kept at −80°C until all the samples were tested. Samples were analyzed using commercial kits by micro-ELISA (Wuhan Elabscience Biotechnology Co. Ltd, China, LOT number WIKYLAGHTI).

Statistical analyses

The SPSS 20.0 statistics program was used to conduct the statistical analysis (IBM Corp., Armonk, NY, USA). For descriptive statistics, the mean, standard deviation, and frequency were applied. The groups were compared using the independent sample t-test. The subgroups were compared by using one-way ANOVA. The paired sample t-test was performed for comparison of the findings in the study group before and after the therapy. Correlation analysis was done by using Pearson's correlation analysis. The cut-off value, sensitivity, and specificity were determined using ROC analysis. The statistical significance was set at $p < 0.05$ and the confidence interval was set as 95%.

Results

The study and control group had mean ages of 11.30±3.11 and 12.42±2.75 years, respectively (p=0.161). There was a slight female dominance in both groups (53.3% of patients and 57.7% of the controls) (p=0.743).

The laboratory and clinical findings of the patients are shown in Table I. The distribution of carditis on admission was: 40% mild, 36.7% moderate, 23.3% severe. After treatment, there were no patients with severe carditis, and mild carditis was observed in 23 patients (76.7%).

Table I. Findings of the study group according to the diagnostic criteria.

	n (%)
Carditis	30 (100%)
Mild	12 (40%)
Moderate	11 (36.6%)
Severe	7 (23.4%)
Arthritis	16 (53.3%)
Fever	27 (90%)
Sydenham Chorea	2 (6.6%)
Elevated ESR and/or CRP	30 (100%)
Elevated ASO titres	25 (83.3%)
Positive throat culture for group A β-hemolytic streptococcus	13 (43.3%)
First degree AV block	16 (53.3%)

ESR: erythrocyte sedimentation rate CRP: C-reactive protein ASO: anti-streptolysin O

The mean CRP levels and ESR of the patients on admission were high (p<0.01).

The mean galectin-3 levels of patients on admission (7.18 ± 8.31 ng/ml) and after the treatment (22.29 ± 19 ng/ml, p<0.001) was significantly different. Figure 1 represents the distribution of galectin-3 levels of the patients on admission and the controls. The mean galectin-3 levels were significantly different by means of the severity of carditis (p=0.006). Mean galectin-3 levels were significantly higher in cases with mild carditis in comparison to ones with severe (p=0.012) and moderate (p=0.028) carditis. Severity of carditis and galectin-3 levels were negatively correlated (r=-539, p=0.02). Levels of galectin-3 in subgroups of the patients on admission are shown in Figure 2.

The mean galectin-3 levels of the cases with arthritis before and after the treatment were 8.41 ±8.73 ng/ml and 18.81 ±16.86 ng/ml, respectively. The mean galectin-3 levels of the cases without arthritis on admission and after the treatment were 5.76 ± 7.88 ng/ml and 26.26 ± 21.09 ng/ml, respectively. There was no significant difference between subgroups regarding the presence of arthritis before and after the treatment (p=0.523, p=0.873, respectively).

The whole study group's mean galectin-3 level was significantly lower than the control before the treatment (p =0.02) but, there was no significant difference after the treatment (p=0.714). Similarly, all except mild carditis had significantly lower levels of galectin-3 than the control group on admission, but mean galectin-3 levels were similar after treatment (Table II). Also, when the mean galectin-3 levels of subgroups defined by the presence of arthritis were compared with the control group, both subgroups had significantly lower mean galectin-3 levels (p=0.001 and p=0.002) than the controls on admission. The mean galectin-3 levels of the patients after treatment were not

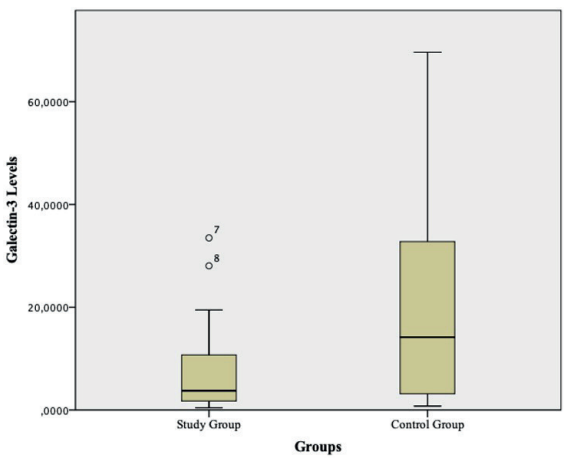

Fig. 1. The distribution of galectin-3 levels of the study group at the time of diagnosis and the control group.

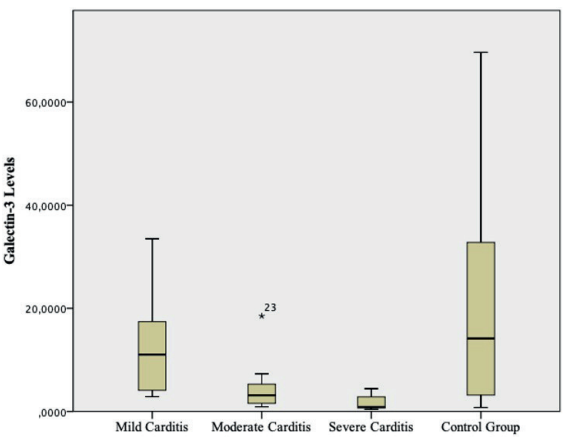

Fig. 2. The distribution of galectin-3 levels according to the severity of carditis at the time of diagnosis and the control group.

Table II. The comparison of mean galectin-3 levels of the study group and the control group.

Patient Group (n:30)		P value*	Control Group (n:26)	P value**
Before Treatment		***0.006***		
Mild carditis	12.6 ± 10.03			0.222
Moderate carditis	4.66 ± 5.05			***0.015***
Severe carditis	4.41 ± 1.81			***0.021***
All	7.18 ± 8.31		20.09 ± 19.59	***0.002***
After Treatment		0.995		
Mild carditis	22.73 ± 15.22			0.718
Moderate carditis	21.99 ± 13.83			0.808
Severe carditis	21.99 ± 31.62			0.862
All	22.29 ± 18.99		20.09 ± 19.59	0.714

Galectin-3 levels are expressed as mean±standart deviation and ng/ml. P values indicate the significance of the differences of galectin-3 levels *within the before and after treatment groups in relation to severity of carditis, and **compared to the control group. Bold italics indicate P < 0.05

significantly different when compared with the controls. One of our patients who had the most severe carditis and required treatment in the intensive care unit due to ARF with valve involvement and ventricular tachycardia had the lowest galectin-3 level (0.3 ng/ml) before treatment and the highest level (69 ng/ml) after treatment when compared with whole subjects.

ROC curve analysis determined a value of 5.46 ng/ml as a cut-off value for galectin-3 with a specificity of 65.4% and a sensitivity of 63.3% for the presence of carditis (Fig. 3).

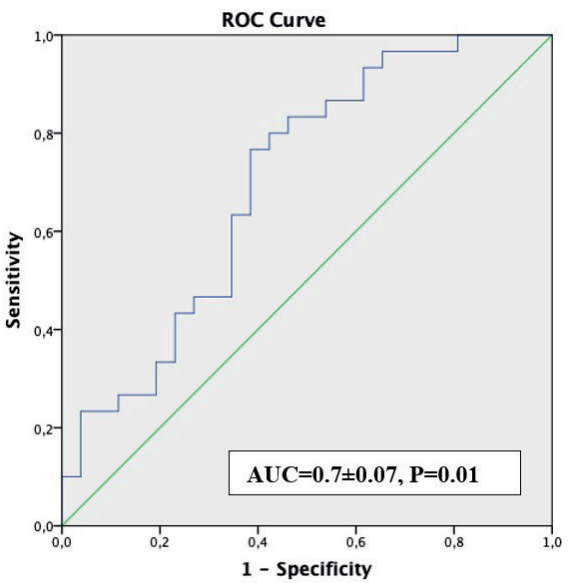

Fig. 3. ROC curve analysis of galectin-3 levels.

Discussion

Acute rheumatic fever is still common in low income countries and major cause of morbidity in our country. Galectin-3 is a biomarker used for various diseases including heart failure.

Acute rheumatic fever is most prevalent between the ages of 5-14 years and in the female gender (1.5-2 times higher risk).[17-19] The ages of the patients were between 6-17 years and 53.3% of them were female, in our study. Sydenham chorea, arthritis/polyarthralgia, fever and carditis was detected in 6.6%, 53.3%, 90% and 100% of patients, respectively. We did not observe any subcutaneous nodules or erythema marginatum. All cases had elevated levels of ESR and CRP on admission. The frequency of mild, moderate and severe carditis was 40%, 36.6% and 23.4%, respectively.

Fifteen galectins have been defined and galectin-3 is the only chimeric member found in humans.[20] It is found in various tissues in humans, but its expression varies according to the tissue type. Galectin-3 has intracellular and extracellular components which both regulate functions related to growth and development whereas extracellular galectin-3 also takes a role in homeostasis.[21] Galectin-3 plays role in inflammation with its both anti-inflammatory and pro-inflammatory properties which are determined according to the type of stimuli and the tissue.[22]

Galectin-3 has extensively been studied in diseases that affect various systems because of its unique properties.[9-13] It was shown to be an indicator of increased risk of heart failure, arrhythmias, atherosclerosis, and the severity of heart diseases.[14] Measurement of galectin-3 levels in patients with heart failure has been recommended in guidelines.[23] It's levels are reported to be low in a normal healthy heart and its expression increases in both chronic and acute decompensated heart failure. Although at the initial phases of heart failure it has a protective role, it leads to adverse remodeling and fibrosis over time.[20,24] In contrast to N-terminal pro-BNP, galectin-3 levels do not decrease rapidly with the resolution of the volume overload.[24] The natriuretic peptides are increased during hemodynamic stress; however, activated macrophages secrete galectin-3 which is associated with inflammation and ventricular remodeling. In contrast to BNP, galectin-3 do not decrease during heart failure in patients with total artificial hearts or ventricular assist devices.[24]

Considering previous data about the role of galectin-3 in cardiovascular diseases and heart failure, while planning this study we hypothesized that galectin-3 may be significantly higher in children diagnosed with ARF. But unexpectedly and surprisingly, the analysis and interpretation of the study data revealed that galectin-3 levels were significantly lower in children with ARF than the controls and this difference disappeared after the treatment. As supporting evidence of these findings, there was a significant difference in galectin-3 levels between subgroups that were determined according to severity of carditis. Patients with mild carditis had higher levels than the ones with moderate and severe carditis, and severity of carditis and galectin-3 levels were negatively correlated. ROC curve analysis determined a cut-off value of 5.46 ng/ml for galectin-3 with a specificity of 65.4% and a sensitivity of 63.3% for the presence of carditis in ARF.

Upon these findings, we searched the literature for decreased levels of galectin-3 in cardiovascular diseases, but we failed to find any report. Although there are some controversies, significantly decreased levels of galectin-3 have been reported in schizophrenia.[25] Galectin-1 and galectin-3 levels have been studied in patients with rheumatoid arthritis, and galectin-1 levels have been reported to be significantly increased.[22] In the same study, galectin-3 levels were significantly decreased, and were not correlated with the erythrocyte sedimentation rate as similar to our study. But in contrast to our study, they found a positive linear trend between galectin-3 levels and disease activity. Their findings were partly in contrast to previous studies, and they concluded that this difference should have resulted from the fact that patients in the study group were taking medication for rheumatoid arthritis. We performed further statistics to analyze any relation between galectin-3 and arthritis, but no correlation was detected. Galectin-3 has been found to be significantly decreased in diffuse cutaneous systemic sclerosis than in limited ones and healthy controls.[26,27]

Although most children will be exposed to group A Streptococcus, ARF develops in only a proportion and this is explained by the genetic susceptibility of the host.[28] Although the exact mechanism is not well established, molecular mimicry is thought to be the main reason. ARF may affect multiple tissues but cardiac involvement is the mainstay of the disease.[29] The similarity between exogenous proteins and human tissues is defined as molecular mimicry.[30] The innate immune system is activated after streptococcal pharyngeal infection, and then the bacterial antigens are presented to T cells. The activation of cellular and humoral immune responses leads to production of cross-reactive antibodies. Carditis is thought to be caused by these cross-reactive antibodies and T cells.[29] Although the pathogenesis of ARF may be related with numerous bacterial antigens, N-acetylglucosamine and M protein are the main epitopes accused of cardiac damage because of the similarity between the alpha-helical structure of the M protein and N-acetyl-beta-D-glucosamine to cardiac myosin.[31]

Galectin-3 mediates many processes during acute inflammation. It has both anti-inflammatory and pro-inflammatory roles. It can bind galactosides.[8] Galectins act as regulators of innate and adaptive immunity and they also have immunomodulatory properties.[32,33] Galectins have been shown to provide innate immunity against blood group molecular mimicry.[34,35] Also, they can recognize the antigenic determinants on the microbes and the host cells. Interestingly they can selectively damage the microbes with the same antigenic determinants but not the human cells. Galectin-4 and galectin-8, are shown to, recognize and destroy human blood group antigen-expressing *Escherichia coli*, and the C-terminal domains mediate this activity. This property of galectins is proposed to protect against molecular mimicry.[35] The regulatory role of galectins in immune response and the protection they provided against molecular mimicry can be the reason for lower levels of galectin-3 in patients with ARF in which the cardiac damage is thought to be mediated by molecular mimicry.

To us, this is the only study focusing on galectin-3 levels in ARF. Our study itself is not able to show the definite role of galectin-3 in ARF absolutely and to highlight the molecular mechanisms leading to decreased levels of galectin-3 in ARF. We think that the decreased levels of this biomarker in ARF are mainly due to its role in inflammation, its pro/anti-inflammatory role, and the protection it provided against molecular mimicry. Although our findings point to it being negatively correlated with the severity of carditis, this correlation may be through the severity of inflammation, rather than heart failure. If it was through heart failure, we might expect to observe increased levels of galectin-3 as stated in the literature. Unfortunately, there isn't any available data about galectin levels with valvular heart diseases although the main pathology in ARF is valvulitis. Further studies will help to highlight the role of this biomarker, in the pathophysiology, severity, and prognosis of the disease. The lowest galectin-3 level at the time of diagnosis and the highest level after treatment was seen in a 7-year-old male patient which was previously published as a case report.[36] Among all cases, he was the case with the most severe carditis (involving 4 valves and ventricular tachycardia). We think that this is supportive evidence that galectin-3 levels decrease in the acute period of rheumatic carditis and becomes to normal values after the treatment.

The study has certain limitations. The sample size is not large enough. Two measurements consisting of before and after treatment were performed rather than serial measurements which might give more reliable data.

In conclusion, children with ARF have significantly reduced levels of galectin-3 and its levels and the severity of the carditis are negatively correlated. In addition, after the treatment, galectin-3 levels return to normal values. More studies with serial measurements of galectin-3 would give more information and molecular studies may highlight the role of galectin-3 in ARF. We think that our study will lead to further studies that will make new contributions to the role of galectin-3 in cardiac diseases.

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Ethical approval

Ethical approval was obtained from Van Training and Research Hospital ethical committee. (Date: 04.10.2018 / No: 2018/14). All procedures performed were in accordance with the ethical standards and with the 1964 Helsinki Declaration and its later amendments.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: SE, MGR; data collection: MGR, ZKE; analysis and interpretation of results: SE, AKB; draft manuscript preparation: MGR, ZKE. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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