Pentraxin 3 levels and correlation with disease severity in patients with acute rheumatic fever

Dolunay Gürses¹, Merve Oğuz², Münevver Yılmaz³, Hülya Aybek³, Funda Akpınar⁴

¹Department of Pediatric Cardiology, Pamukkale University Faculty of Medicine, Denizli, Turkey
²Department of Pediatrics, Pamukkale University Faculty of Medicine, Denizli, Turkey
³Department of Biochemistry, Pamukkale University Faculty of Medicine, Denizli, Turkey
⁴Department of Developmental and Behavioral Pediatrics, Ankara University Faculty of Medicine, Ankara, Turkey

ABSTRACT

Objectives: This study aims to investigate serum pentraxin 3 (PTX3) levels during acute episode of acute rheumatic fever (ARF) and their relationship with disease severity.

Patients and methods: The prospective study was conducted between January 2015 and December 2018 and included 52 ARF patients (22 girls, 30 boys, mean age 10.7±2.1 years; range, 5 to 16 years) experiencing an acute episode and 22 healthy children (13 girls, 9 boys, mean age 10.3±3.8 years; range, 5 to 16 years). ARF patients were classified into three groups based on the clinical course: isolated arthritis (n=17), mild carditis (n=19), and moderate/severe carditis (n=16). Blood samples were collected from all patients before treatment and from the healthy children in the control group to measure PTX3 levels. PTX3 was measured using sandwich enzyme-linked immunosorbent assay method.

Results: Plasma PTX3 levels were significantly higher in ARF group compared to the control group (4.7±5.2 and 1.2±1.7 ng/mL, p<0.001). Subgroup analysis of serum PTX3 levels in ARF patients with isolated arthritis, mild carditis, and moderate/severe carditis (3.2±3.1 ng/mL, 4.3±5 ng/mL, and 6.7±6.6 ng/mL, respectively) showed that serum PTX3 was significantly higher in the moderate/severe carditis group compared to the other groups (p<0.05). Analysis of echocardiographic data showed that serum PTX3 was positively correlated with left ventricular end-diastolic diameter, left atrial diameters, and mitral A velocity and negatively correlated with E/A ratio (p<0.05; r=0.231, 0.402, 0.562, -0.586, respectively).

Conclusion: High PTX3 level during an acute episode of ARF may help predict the clinical course and the severity of accompanying carditis. However, prospective studies with larger sample sizes are needed.

Keywords: Acute rheumatic fever, child, pentraxin 3.
the clearance of apoptotic cells, modulation of inflammation and angiogenesis, and formation of extracellular matrix. It belongs to the same protein family as C-reactive protein (CRP); however, while CRP is mainly synthesized in the liver, PTX3 is mostly produced locally in the area of inflammation. PTX3 has been associated with inflammation in cardiovascular diseases such as heart failure, atherosclerosis, acute coronary syndrome, peripheral vascular diseases, and rheumatic mitral valve stenosis. To our knowledge, there are no previous studies in the literature regarding serum PTX3 levels in ARF patients. In this study, we aimed to investigate serum PTX3 levels during acute episode of ARF and their relationship with disease severity.

PATIENTS AND METHODS

This prospective study was conducted in the Pediatric Cardiology Department of Pamukkale University Faculty of Medicine between January 2015 and December 2018. The study group consisted of 52 patients (22 girls, 30 boys, mean age 10.7±2.1 years; range, 5 to 16 years) with acute ARF episode. ARF was diagnosed based on the modified Jones criteria. The 2002 version of the modified Jones criteria was used until the year 2016, while the 2015 updated version was used after the year 2016. Patients with recurrent ARF were excluded. Valve involvement in ARF patients was evaluated based on the 2012 World Heart Federation Rheumatic Carditis criteria. ARF patients were classified into three groups based on the clinical course of the acute episode: isolated arthritis (n=17), mild carditis (n=19), and moderate/severe carditis (n=16).

The control group consisted of 22 voluntary, age- and sex-matched healthy children (13 girls, 9 boys, mean age 10.3±3.8 years; range, 5 to 16 years) with no history of hypertension, renal or cardiac diseases. Children in the control group had normal physical examination, biochemical analysis and echocardiographic evaluation. Children who had received nonsteroidal anti-inflammatory drugs were excluded. There were no other systemic or cardiovascular diseases that could affect serum PTX3 level. The study protocol was approved by the Pamukkale University Faculty of Medicine Ethics Committee (Approval No: 60116787-020/53183).

A written informed consent was obtained from parents of all patients and control subjects. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Blood samples were collected from the children diagnosed with ARF before treatment and from the healthy children in the control group to measure PTX3 levels. After centrifugation, samples were stored at -80°C. Serum PTX3 levels were measured using a sandwich enzyme-linked immunosorbent assay kit (Bioassay Technology, Shanghai, China, Catalog no: E1938Hu). Absorbance values at a wavelength of 450 nm were measured using a BioTek-Elx800 Absorbance Microplate Reader (BioTek Instruments Inc., Winooski, VT, USA) and PTX3 concentrations were calculated. Sensitivity of the assay for PTX3 is <0.05 ng/mL.

All ARF patients and control subjects underwent two-dimensional, motion-mode (M-mode), and Doppler examination with GE Vingmed Vivid 7 echocardiography (GE Vingmed, Ultrasound AS, Horten, Norway) and multifrequency transducer (2.5-4 MHz). Images were acquired without sedation, with children in left lateral decubitus position. The mean of three consecutive measurements was recorded. M-mode measurements were performed at the level of the tips of the mitral valve leaflets in the parasternal long-axis view of the left ventricle (LV). Standard parameters measured in parasternal long-axis by M-mode echocardiography included left ventricular end-diastolic diameter (LVEDD), interventricular septum thickness at end-diastole (IVSTd), and left ventricular posterior wall thickness at end-diastole (LVPWTd). Left ventricular ejection and shortening fractions (LVEF, LVSF) were calculated as described previously. Pulsed wave Doppler blood velocities were measured for the mitral valve using apical four-chamber view (peak E and A wave) and E/A ratio was determined.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation, median (interquartile range) and qualitative variables as number (percentage). Kolmogorov-Smirnov and Shapiro-Wilk tests were used for determination of normal distribution. For independent groups
|                          | ARF group (n=52) | Control group (n=22) | p     |
|--------------------------|------------------|----------------------|-------|
|                          | n    | Mean±SD | Min-Max | Median | IQR          | n | Mean±SD | Min-Max | Median | IQR          |
| Age (year)               |      | 10.7±2.1 | 5-16    | 11     | 9.12         |    | 10.3±3.8 | 5-16    | 10.5   | 6.7-14      | >0.05*|
| Sex                      |      |          |         |        |              | Male | 30 | 9.3±1.5  | 5-13    | 10      | 9.5-11.5   | >0.05**|
|                          |      |          |         |        |              | Female | 22 | 11.2±1.9 | 8-14    | 11.2    | 10.8-11.6  | >0.05*** |
| Weight (kg)              |      | 41.5±12.8 | 20-71   | 41.5   | 31.51.5      |    | 37.9±17.4 | 18-70    | 31     | 22.7-54.2  | >0.05*|
| Height (cm)              |      | 144.9±13 | 112-169 | 145.5  | 135.2-156    |    | 140±22.6 | 107-175 | 139    | 118.7-163.5| >0.05*** |
| BMI (kg/m²)              |      | 19.3±3.9 | 12.3-28.1 | 19.6 | 16-21       |    | 18.2±3.3 | 14.3-24.8 | 17.4   | 15.7-19.4  | >0.05*|
| Heart rate (beats/min)   |      | 81.4±4.7 | 75-100 | 80     | 78.84       |    | 80.8±5.5 | 72-95   | 80     | 78.8-95    | >0.05*|
| Systolic blood pressure  |      | 108.4±10.6 | 89-130 | 110    | 100-115     |    | 105.8±9.9 | 90-125  | 107    | 95.7-115   | >0.05*|
| Diastolic blood pressure |      | 65.2±9.1 | 47-90   | 65     | 60-75       |    | 65.2±9.1 | 50-85   | 65     | 58.7-72.5  | >0.05*|
| WBC count (/mm³)         |      | 11.35±3.327 | 6.610-22.400 | 10.870 | 8.615-13.262 |    | 7.906±1.813 | 3.370-10.080 | 8.325 | 6.895-9.290  | 0.000*|
| Hemoglobin (g/dL)        |      | 11.6±1    | 9.1-14 | 11.6   | 11-12.3     |    | 12.4±0.7 | 11.4-14.1 | 12.2   | 11.8-12.9  | 0.003***|
| Platelet count (/mm³)    |      | 422,000±133,330 | 166,000-705,000 | 412,500 | 325,750-530,000 | 284,955±45,034 | 210,000-380,000 | 280,000 | 247,000-330,000 | 0.000***|
| CRP (mg/dL)              |      | 8.8±6.6   | 2-27   | 6.8    | 3-12.8      |    | 0.14±0.14 | 0.03-0.5 | 0.06   | 0.05-0.2   | 0.000*|
| ESR (mm/h)               |      | 80.4±22.6 | 36-130 | 76     | 62-299.5    |    | 14.3±4.4 | 8-22    | 14     | 10-18       | 0.000***|
| Fibrinogen (mg/dL)       |      | 662.6±352 | 249-2918 | 639.5 | 500-7752.2  |    | 234.6±23 | 188.286 | 238   | 220-248    | 0.000*|
| ASO (IU/mL)              |      | 968.9±630.4 | 113-386 | 893    | 557-1150    |    | 60±38.6 | 4-122   | 54     | 21.5-99.5  | 0.000*|
| Pentraxin 3 (ng/mL)      |      | 4.7±5.2   | 0.16-18.9 | 2.78 | 0.50-7.25   |    | 1.2±1.7 | 0.1-5.8  | 0.41   | 0.11-1.15  | 0.000*|

ARF: Acute rheumatic fever; SD: Standard deviation; Min: Minimum; Max: Maximum; IQR: Interquartile range; BMI: Body mass index; WBC: White blood cell; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; ASO: Anti-streptolysin O; * Mann-Whitney U test; ** Chi-square test; *** Independent-samples t-test.
### RESULTS

There was no statistically significant difference in terms of age, sex, weight, height, BMI, heart rate, or blood pressure between isolators arthritis and control groups (p>0.05). The demographic characteristics and laboratory data of the ARF and control groups are shown in Table 1.

### Table 2. Demographic characteristics and laboratory results of arthritis, carditis, and control groups

|                      | Isolated arthritis (n=17) (Group 1) | Carditis (n=35) (Group 2+3) | Control (n=22) (Group 4) |
|----------------------|------------------------------------|----------------------------|--------------------------|
| n                    | Mean±SD                            | Mean±SD                    | Mean±SD                  |
| Age (years)          | 10.5±1.5                           | 10.8±2.4                   | 10.3±3.8                 |
| Sex                  | 13                                 | 17                         | 9                         |
| Male                 | 13                                 | 17                         | 9                         |
| Female               | 4                                  | 18                         | 13                        |
| Weight (kg)          | 37.6±10                            | 41.4±13.7                  | 37.9±17.4                |
| Height (cm)          | 144.3±9.9                          | 135.5±132                  | 187.0                    |
| BMI (kg/m²)          | 17.8±3.5                           | 15.3±20.7                  | 140.2±22.6               |
| Heart rate (beats/min) | 86.3±11                            | 76.46                      | 80.4±5.2                 |
| Systolic blood pressure | 106.9±107                        | 109.2±106                  | 90.8±99                  |
| Diastolic blood pressure | 64.8±9.8                          | 62.3±10.1                  | 66.3±7.0                 |
| WBC count (×10⁹/L)   | 10,663±3272                        | 11,688±3,117               | 7,960±1,831              |
| Hemoglobin (g/L)     | 12±0.9                             | 11.5±1                     | 11.25±1                  |
| Platelet count (×10⁹/L) | 422,769±336,612                    | 421,671±337,26             | 321,000±548,000          |
| CRP (mg/L)           | 8.2±3.3                            | 9.6±8                      | 2.3±1                    |
| ESR (mm/h)           | 75.5±214                           | 82.8±231                   | 39.1±10                  |
| Fibrinogen (mg/dL)   | 577.6±363.9                        | 703.9±409.6                | 650±20                   |
| ASO (IU/mL)          | 959.6±682                          | 973.7±64.3                | 907±75                   |
| PTX3 (ng/mL)         | 3.2±3.1                            | 4.3±5.9                    | 5.4±5.9                  |

**Note:** ARF: Acute rheumatic fever; SD: Standard deviation; Min: Minimum; Max: Maximum; IQR: Interquartile range; BMI: Body mass index; WBC: White blood cell; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; ASO: Antistreptolysin O; * Chi-square test; † One-way analysis of variance test; ‡ Kruskal-Wallis test.
### Table 3. Demographic characteristics and laboratory results of arthritis, mild carditis, moderate/severe carditis, and control groups

|                              | Isolated arthritis (n=17) (Group 1) | Mild carditis (n=19) (Group 2) | Moderate/severe Carditis (n=16) (Group 3) | Control (n=22) (Group 4) |
|------------------------------|--------------------------------------|-------------------------------|---------------------------------------------|--------------------------|
| **Mean±SD (Min-Max)**        |                                      |                               |                                              |                          |
| Age (year)                   | 10.5±1.5 (8-13)                      | 10.6±2.4 (5-14)               | 11±2.4 (5-16)                               | 10.3±3.8 (5-16)          |
| Sex (n)                      | 13 Male / 4 Female                   | 9 Male / 10 Female            | 8 Male / 8 Female                            | 9 Male / 13 Female       |
| Weight (kg)                  | 37.6±10 (21-57)                      | 44.6±13.6 (20-71)             | 41.8±13.6 (20-71)                           | 37.9±17.4 (18-70)        |
| Height (cm)                  | 144.3±99 (129-162)                   | 147.5±13.7 (112-164)         | 142.5±15.1 (115-169)                        | 140±22.6 (107-175)       |
| BMI (kg/m²)                  | 17.8±3.5 (12.3-25.3)                 | 20.1±4 (12.8-28)              | 20.3±3.9 (14.8-28.2)                        | 18.2±3.3 (14-24.8)       |
| Heart rate (beats/min)       | 81.8±3.1 (76-86)                     | 79.4±3.7 (75-85)              | 83.2±6.2 (78-100)                           | 80.8±5.2 (78-84)         |
| Systolic blood pressure      | 106.9±10.7 (89.130)                  | 106.6±10 (89-130)             | 109±11 (90-110)                             | 105.8±9.9 (90-125)       |
| Diastolic blood pressure     | 64.8±9.4 (47-80)                     | 67.2±10.1 (50-70)             | 69.3±10.2 (55-90)                           | 65.2±9.1 (50-85)         |
| WBC count (/mm³)             | 1066x3727 (6610-22400)               | 11335x3047 (6880-18000)       | 121073x2747 (7894-18200)                     | 7906x1813 (3307-1008)    |
| Hemoglobin (g/dL)            | 12±0.9 (10.5-13.7)                   | 11±0.8 (10.3-13.3)            | 11±1.2 (9.14-11.2)                          | 12±0.7 (11.4-11.2)       |
| Platelet count (/mm³)        | 422706±136612 (177000±701000)        | 394158x136485 (209000±705000) | 454313x136485 (166000-657000)                | 284955x45034 (210000-380000) |
| CRP (mg/dL)                  | 8.2±6.3 (2.4-24)                     | 9.6±5.5 (2.8-27)              | 9.7±3.8 (2.5-22)                            | 9.8±4.0 (2.5-13.6)       |
| ESR (mm/h)                   | 75.2±21.4 (36-115)                   | 80±22.4 (39-119)              | 85±24.4 (51-130)                            | 14±3±4 (9-22)            |
| Fibrinogen (mg/dL)           | 577.6±163.9 (340-826)                | 621.5±123.3 (410-884)        | 801.7±586 (540-700)                         | 234±6±2 (188-286)        |
| ASO (IU/mL)                  | 959±548.2 (243±229.9)                | 1109.5±792 (289-3862)        | 812.5±46.4 (113-1983)                       | 60.3±8.6 (41-125)        |
| Pentraxin 3 (ng/mL)          | 3.2±3.1 (0.2-10.08)                  | 4.3±5 (0.16-15.4)             | 6.7±6.6 (0.23-18.9)                         | 1.2±1.7 (0.15-5.8)       |
| LVPWTD (cm)                  | 0.81±0.1 (0.6-1)                     | 0.8±0.15 (0.6-1)              | 0.8±0.1 (0.7)                              | 0.7±0.12 (0.6-1)         |
| LVEDD (cm)                   | 4.14±0.43 (3.5-4.9)                  | 4.25±0.46 (3.5-5.3)          | 4.67±0.51 (4.15-5.5)                        | 3.9±0.45 (3.3-4.7)       |
### Table 3. Continued

|                          | Isolated arthritis (n=17) (Group 1) | Mild carditis (n=19) (Group 2) | Moderate/severe carditis (n=16) (Group 3) | Control (n=22) (Group 4) | p       | Significant group comparisons |
|--------------------------|-------------------------------------|---------------------------------|------------------------------------------|--------------------------|---------|------------------------------|
|                          | Mean±SD (Min-Max)                   | Mean±SD (Min-Max)               | Mean±SD (Min-Max)                        | Mean±SD (Min-Max)        |         |                              |
| IVSTd (cm)               | 0.82±0.1 (0.6-1)                    | 0.78±0.12 (0.6-1)               | 0.80±0.11 (0.6-1)                        | 0.79±0.11 (0.6-1)        | >0.05‡  |                              |
| LAD (cm)                 | 2.85±0.29 (2.3-3.3)                 | 2.8 (2.6-3.1)                   | 3.4±0.38 (2.8-4)                         | 2.6±0.36 (2.3-3)         | 0.000†  | 1-3, 2-3, 2-4, 3-4           |
| LVEF (%)                 | 80.6±4.1 (72-86)                    | 81.3 (77.8-84.6)                | 76.7±4.7 (64-83)                         | 80.7±3.8 (72-88)         | >0.05†  |                              |
| LVSF (%)                 | 42.4±4.1 (34.8-48.9)                | 42.8 (38.6-46.4)                | 40.9±5 (32.4-48.9)                       | 42.4±3.8 (34.7-51)       | >0.05†  |                              |
| Mitral E (m/s)           | 99.4±10.5 (82-118)                  | 101 (89-108.5)                  | 96.6±9.4 (78-110)                        | 96.8±9.1 (76-112)        | >0.05†  |                              |
| Mitral A (m/s)           | 48.6±7.6 (38-62)                    | 48 (42.5-54.5)                  | 49.1±10.1 (34-67)                        | 55.9±10.5 (41.7-67)      | 0.011†  | 3-4                          |
| E/A ratio                | 2±0.22 (1.512-4.2)                  | 2.1 (1.96-2.22)                 | 2±0.29 (1.6-2.54)                        | 1.77±0.24 (1.37-2.24)    | 0.003†  | 1-3, 2-3, 3-4, 4-5           |

SD: Standard deviation; Min: Minimum; Max: Maximum; IQR: Interquartile range; BMI: Body mass index; WBC: White blood cell; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; ASO: Antistreptolysin O; LVPWTd: Left ventricular posterior wall thickness at diastole; LVEDD: Left ventricular end-diastolic diameter; IVSTd: Interventricular septum thickness at diastole; LAD: Left atrium diameter; LVEF: Left ventricular ejection fraction; LVSF: Left ventricular shortening fraction; Mitral E: Mitral early diastolic flow rate; Mitral A: Mitral late diastolic flow rate; * Chi-square test; † One-way analysis of variance test; ‡ Kruskal-Wallis test.
PTX3 level was higher in the carditis group than the other groups, while the difference between the carditis and control groups was statistically significant (p<0.05) (Table 2).

Of 35 ARF patients with carditis, 10 (28.5%) had mitral valve insufficiency alone, two (6%) had aortic valve insufficiency alone, and 23 (65.5%) had both aortic and mitral valve insufficiency. None of the patients had mitral valve stenosis. Nineteen (54%) patients had mild carditis and 16 (46%) had moderate/severe carditis. There were no statistically significant differences between the arthritis, mild carditis, moderate/severe carditis, and control groups in terms of age, sex, weight, height, BMI, heart rate, or blood pressure (p>0.05) (Table 3). Platelet count, ESR, and CRP, fibrinogen, and ASO levels were significantly higher in the arthritis, mild carditis, and moderate/severe carditis group compared to the control group (p<0.001). WBC count was higher and hemoglobin level was lower in the mild carditis and moderate/severe carditis groups than the control group (p<0.05). The mean serum PTX3 level was 1.2±1.7 (range, 0.1 to 5.8) ng/mL in the control group, 3.2±3.1 (range, 0.3 to 10.1) ng/mL in the isolated arthritis group, 4.3±5 (range, 0.2 to 15.4) ng/dL in the mild carditis group, and 6.7±6.6 (range, 0.2 to 18.9) ng/dL in the moderate/severe carditis group. Although serum PTX3 levels were higher in all patient groups when compared with the control group, the differences were significant only in the mild and moderate/severe carditis groups (p<0.05) (Table 3) (Figure 1).

In echocardiographic analysis, no difference was detected between the groups in terms of LVPWTd, IVSTd, LVEF, or LVSF values (p>0.05). LVEDD and left atrial diameters (LAD) were significantly higher in the moderate/severe carditis group compared to all other groups (p<0.001). No difference was detected between the groups in terms of mitral valve E-wave velocity (p>0.05), while mitral valve A-wave velocity was significantly higher in the moderate/severe carditis group than in the control group (p<0.05) and E/A ratio was significantly lower in the moderate/severe carditis group compared to the other groups (p<0.05).

Figure 1. Serum pentraxin 3 levels of arthritis, mild carditis, and moderate/severe carditis acute rheumatic fever subgroups and control group.
PTX3: Pentraxin 3; * Effective values.

Figure 2. Positive correlation between serum pentraxin 3 level and left ventricular end-diastolic diameter.
LVEDD: Left ventricular end-diastolic diameter; PTX3: Pentraxin 3.

Figure 3. Positive correlation between serum pentraxin 3 level and left atrial diameters.
LAD: Left atrial diameters; PTX3: Pentraxin 3.
The CRP level was positively correlated with WBC and platelet count, ESR, and fibrinogen level, and negatively correlated with hemoglobin level (p<0.05; r values: 0.449, 0.265, 0.691, 0.675, -0.384, respectively). CRP level was also positively correlated with LVEDD and LAD (p<0.05; r values: 0.355, 0.263, respectively).

Serum PTX3 level was positively correlated with platelet count, ESR, and fibrinogen level and negatively correlated with hemoglobin level (p<0.05, r values: 0.416, 0.338, 0.324, -0.238, respectively). Analysis of echocardiographic data showed that PTX3 level was positively correlated with LVEDD, LAD, and mitral valve A-wave velocity and negatively correlated with E/A ratio (p<0.05; r values: 0.231, 0.402, 0.562, -0.586, respectively). The correlations between serum PTX3 levels and LVEDD, LAD, mitral A-wave velocity, and E/A are visualized in Figures 2, 3, 4, and 5.

**DISCUSSION**

Acute rheumatic fever is an autoimmune disease caused by the abnormal immune response against streptococcus infections in genetically predisposed children. Inflammation in ARF involves a series of complicated factors including the cellular and humoral immune systems. There are no specific biomarkers for ARF diagnosis and follow-up; the diagnosis is established clinically based on the Jones criteria. This has prompted research into more specific biomarkers that clinicians can use at the time of diagnosis to determine disease severity and predict cardiac involvement or prognosis. PTX3 is a new-generation acute phase reactant that is structurally related to CRP and serum amyloid P, and its role in the inflammatory process is still under investigation. Our study is important because it is the first in the literature to evaluate serum PTX3 levels in ARF patients during an acute episode. The serum PTX3 levels were found to be increased in ARF patients when compared to healthy children in our study. In addition, the PTX3 levels were higher in mild and moderate/severe carditis groups.

The two most important characteristics of PTX3 are that it is locally produced in the endothelium and it reaches peak levels faster than CRP. It is reported that PTX3 level is elevated in cardiovascular diseases and can be regarded as a biomarker of cardiovascular disease in the general population. High serum PTX3 levels have also been associated with increased cardiovascular complications in conditions such as Cushing’s and Behçet’s diseases and in hemodialysis patients. In addition, there are studies on its potential superiority to CRP as a biomarker of cardiovascular disease due to its
rapid response and ability to reflect vascular inflammation. In a study conducted with childhood-onset systemic lupus erythematosus patients, it was found that serum PTX3 levels significantly increased in the presence of vasculitis, and it was reported that serum PTX3 levels could be useful in detecting subclinical vascular involvement. In another study, serum PTX3 levels were found to be higher in patients with juvenile scleroderma than healthy controls, but there was no correlation with vascular complications. However, a positive correlation was found between serum PTX3 level and skin thickening and fibrosis. In our study, CRP levels were higher in all ARF subgroups (arthritis and carditis) compared to the control group, while PTX3 level was only significantly higher in patients with carditis compared to healthy controls. These findings support the view that PTX3 may be a more specific biomarker than CRP in vascular inflammation and that high serum PTX3 levels may predict carditis in ARF patients. In the future steps of our study, evaluating the relationship between serum PTX3 levels during an acute episode and rheumatic heart disease, which is a chronic complication of the ARF, may be a guide in explaining the relationship between PTX3 and fibrosis development.

Studies on PTX3-deficient mouse models demonstrated greater ischemia/reperfusion-induced cardiac damage after myocardial infarction and increased atherosclerotic lesions with a high-fat diet. Therefore, PTX3 is believed to have cardioprotective and atheroprotective effects. On the other hand, Swada et al. reported that although patients with abdominal aortic aneurysm showed no difference in serum PTX3 level, tissue PTX3 expression was increased compared with the control group and was negatively correlated with maximum aorta diameter. We detected no correlation between PTX3 and carditis severity in the present study. However, similar to the study by Swada et al., future studies evaluating tissue expression of PTX3 in addition to serum PTX3 levels will improve our understanding of the role of PTX3 in the pathogenesis of ARF and its relationship with carditis.

Mitral valve involvement is observed most frequently in ARF, followed by aortic valve involvement. This involvement usually manifests as valve insufficiency during the initial episode. Left side valve insufficiency causes increased volume load and diameter in the left atrium and LV. In our study, left ventricular end-diastolic and LAD were greater in the moderate/severe carditis group than in the other groups due to valve involvement. While no difference was detected between the groups in terms of left ventricular systolic functions, we found that left ventricular late diastolic wave velocity was higher and E/A ratio was lower in the moderate/severe carditis group compared to the other groups. Our results indicate that left ventricular diastolic functions are affected in the moderate/severe carditis group. In their study on individuals with Behçet’s disease, Çalık et al., reported a correlation between serum PTX3 level and LAD and mitral E/A ratio. Similarly, in the present study, serum PTX3 level was positively correlated with left ventricular end-diastolic and LAD and mitral late diastolic pulse wave, and negatively correlated with E/A ratio in patients with acute episode of ARF. Studies evaluating echocardiographic data together with serum PTX3 data in larger series may shed light on the role of PTX3 in the pathophysiology of carditis.

In conclusion, our study is the first to demonstrate elevated serum PTX3 levels in patients during an acute episode of ARF. High serum PTX3 levels may help predict the development of carditis during the course of an acute ARF episode. However, further prospective studies that include larger series are needed.

Declaration of conflicting interests
The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding
This research has been supported by Pamukkale University Research Fund (Number 2018HZP047).
REFERENCES

1. Orün UA, Ceylan O, Bilici M, Karademir S, Ocal B, Senocak F, et al. Acute rheumatic fever in the Central Anatolia Region of Turkey: a 30-year experience in a single center. Eur J Pediatr 2012;171:361-8.

2. Park MK. Acute rheumatic fever. In: Park MK, editor. Park’s Pediatric Cardiology for Practitioners. 6th ed. Philadelphia: Elsevier Saunders; 2014. p. 604-13.

3. Tani LY. Rheumatic fever and rheumatic heart disease. In: Allen HD, Driscoll MD, Shaddy RE, Feltes TF, editors. Moss and Adams’ Heart Disease in Infants, Children, and Adolescents. 8th ed. Philadelphia: Lippincott Williams &Wilkins; 2013. p. 1303-30.

4. Ristagno G, Fumagalli F, Bottazzi B, Mantovani A, Olivari D, Novelli D, et al. Pentraxin 3 in Cardiovascular Disease. Front Immunol 2019;10:823.

5. Blassova T, Tonar Z, Tomasek P, Hosek P, Hollan J, Treska V, et al. Inflammatory cell infiltrates, hypoxia, vascularization, pentraxin 3 and osteoprotegerin in abdominal aortic aneurysms - A qualitative histological study. PLoS One 2019;14:e0224818.

6. Alpaslan Mesci B, İbilgen Bağlık B, Gül Şahin H, Gönenli G, Kavala M, Kasapçıoğlu Günel E, et al. Can pentraxin-3 be a candidate marker in the follow-up of the patients with Behçet’s disease? Arch Rheumatol 2016;32:91-5.

7. Chu Y, Teng J, Feng P, Liu H, Wang F, Li X. Pentraxin-3 in coronary artery disease: A meta-analysis. Cytokine 2019;119:197-201.

8. Wu T, Zhu B, Zhu Q, Tursun D, Liu S, Liu S, et al. Study on serum pentraxin-3 levels in vasculitis with hypertension. J Interferon Cytokine Res 2019;39:522-30.

9. Polat N, Yildiz A, Alan S, Toprak N. Association of pentraxin-3 with the severity of rheumatic mitral valve stenosis. Acta Cardiol 2015;70:409-13.

10. Ferrieri P; Jones Criteria Working Group. Proceedings of the Jones Criteria workshop. Circulation 2002;106:2521-3.

11. Gewitz MH, Baltimore RS, Tani LY, Sable CA, Shulman ST, Carapetis J, et al. Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. Circulation 2015;131:1806-18.

12. Remenyi B, Wilson N, Steer A, Ferreira B, Kado J, Kumar K, et al. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease—an evidence-based guideline. Nat Rev Cardiol 2012;9:297-309.

13. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978;58:1072-83.

14. Silverman NH. Quantitative methods to enhance morphological information using M-mode, Doppler, and cross-sectional ultrasound. In: Silverman NH, editor. Pediatric Echocardiography. Baltimore: Williams and Wilkins; 1993. p. 35-108.

15. Guilherme L, Kalil J. Rheumatic fever and rheumatic heart disease: cellular mechanisms leading autoimmune reactivity and disease. J Clin Immunol 2010;30:17-23.

16. van Rossum AP, Pas HH, Fazzini F, Huijtema MG, Limburg PC, Jonkman MF, et al. Abundance of the long pentraxin PTX3 at sites of leukocytoclastic lesions in patients with small-vessel vasculitis. Arthritis Rheum 2006;54:986-91.

17. Garlanda C, Bottazzi B, Magrini E, Inforzato A, Mantovani A. PTX3, a Humoral pattern recognition molecule, in innate immunity, tissue repair, and cancer. Physiol Rev 2018;98:623-39.

18. Latini R, Maggioni AP, Peri G, Gonzini L, Lucci D, Mocarelli P, et al. Prognostic significance of the long pentraxin PTX3 in acute myocardial infarction. Circulation 2004;110:2349-54.

19. Mancini T, Kola B, Mantero F, Boscaro M, Arnaldi G. High cardiovascular risk in patients with Cushing’s syndrome according to 1999 WHO/ISH guidelines. Clin Endocrinol (Oxf) 2004;61:768-77.

20. Xu Y, Ding X, Zou J, Liu Z, Jiang S, Xu S, et al. Plasma pentraxin 3 is associated with cardiovascular disease in hemodialysis patients. Ren Fail 2011;33:998-1004.

21. Çalık AN, Özcan KS, Mesci B, Çınar T, Çanga Y, Güngör B, et al. The association of inflammatory markers and echocardiographic parameters in Behçet’s disease. Acta Cardiol 2020;75:130-7.

22. Buda V, Andor M, Tomescu MC, Cristescu C, Voicu M, Citu I, et al. P2637 ACE inhibitors and ARBs decrease more powerful the PTX-3 plasma levels of hypertensive patients with endothelial dysfunction compared with other anti-hypertensive drugs, in a chronic treatment, European Heart Journal 2017;38 suppl_1:ehx502.P2637.

23. Naito Y, Tsujino T, Akahori H, Ohyajangi M, Mitsuno M, Miyamoto Y, et al. Increase in tissue and circulating pentraxin3 levels in patients with aortic valve stenosis. Am Heart J 2010;160:685-91.

24. Sahin S, Adrovic A, Barut K, Durmus S, Gelisgen R, Uzun H, et al. Pentraxin-3 levels are associated with vasculitis and disease activity in childhood-onset systemic lupus erythematosus. Lupus 2017;26:1089-94.

25. Adrovic A, Sahin S, Barut K, Durmus S, Uzun H, Kasapcopur O. Significance of pentraxin-3 in patients with juvenile scleroderma. Clin Exp Rheumatol 2017;35 Suppl 106:221-2.

26. Salio M, Chimenti S, De Angelis N, Molla F, Maina V, Nebuloni M, et al. Cardioprotective function of the long pentraxin PTX3 in patients with juvenile scleroderma. J Exp Rheumatol 2008;117:1055-64.

27. Norata GD, Marchesi P, Pulakazhi Venu VK, Pasqualini F, Anselmo A, Moalli F, et al. Deficiency of the long pentraxin PTX3 promotes vascular inflammation and atherosclerosis. Circulation 2009;120:699-708.
28. Sawada H, Naito Y, Oboshi M, Iwasaku T, Morisawa D, Okuhara Y, et al. Pentraxin 3 expression in human abdominal aortic aneurysm. Circulation 2014;130:A15060.

29. Alqanatish J, Alfadhel A, Albelali A, Alqahtani D. Acute rheumatic fever diagnosis and management: Review of the global implications of the new revised diagnostic criteria with a focus on Saudi Arabia. J Saudi Heart Assoc 2019;31:273-81.