Serum Calprotectin like a Potential Serum Biomarker of Aggressive Erosive Course of Juvenile Arthritis

Kozhevnikov AN[1*], Pozdeeva NA[1], Maricheva ON[2], Murashko TV[2], Bogdanova SL[3], Derkach EA[3], Vissarionov SV[4] and Novik GA[5]

[1]Department of Trauma Sequelae and Rheumatoid Arthritis, Saint-Petersburg State Pediatric Medical University, Saint-Petersburg, Russia

[1]Department of Trauma Sequelae and Rheumatoid Arthritis, Saint-Petersburg State Pediatric Medical University, Saint-Petersburg, Russia

[2]Department of Diagnostic Radiology, National Medical Research Center, Saint-Petersburg, Russia

[3] Department of Laboratory Diagnostics, National Medical Research Center, Saint-Petersburg, Russia

[4]Department of Spinal Pathology and Neurosurgery, National Medical Research Center, Saint-Petersburg, Russia

[5]Department of Pediatric, Saint-Petersburg State Pediatric Medical University, Saint-Petersburg, Russia

*Corresponding Author**

Kozhevnikov AN
Department of Trauma Sequelae and Rheumatoid Arthritis,
Saint-Petersburg State Pediatric Medical University,
Saint-Petersburg, *Russia*
E-mail: Rheumaspb@gmail.com

Copyright: 2022 Kozhevnikov AN, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Received: July 26, 2022, Manuscript No. JAHS-22-70400; **Editor assigned:** July 28, 2022, PreQC No. JAHS-22-70400 (PQ); **Reviewed:** August 11, 2022, QC No. JAHS-22-70400; **Revised:** December 21, 2022, Manuscript No. JAHS-22-70400 (R); **Published:** December 29, 2022, DOI: 10.4172/2167-7921.2022.11.058

Abstract

Introduction: Juvenile Arthritis (JA) is an autoimmune inflammatory joint disease. There is no reliable laboratory test for JA. Some researchers reported that the serum levels of calprotectin may be correlated with arthritis activity.

Materials and methods: Level of serum Calprotectin (sCal) was evaluated in 70 children with JIA (50 active JIA/20 inactive arthritis) and 20 adolescents with non-rheumatic joint disease. In comparison the serum level of IL6, TNF-alpha, and vimentin were assessed.

Results: Statistical analysis were revealed a correlation between sCalc and active erosive JA (R^2=0.4159, T=4.336, OR erosive JA=3.3193, 95%CI 1,7006-6.4789, p=0.0079). Serum level of vimentin, IL6 and TNF-alpha were not always correlated with active stage JA and erosive joint damage (p>0,05). The ROC analysis of the sCalc showed that a cutoff point more of 2,9 μg/ml may be high prognostic factor for related erosive JA (AUC 0,837 ± 0,0553, 95% CI 0,711-0.923).

Conclusions: The serum levels of calprotectin are significantly associated with erosive course of JA. These results suggest that calprotectin might be superior to serum IL6 and TNF-alpha for aggressive erosive course of JA.

Keywords: Juvenile arthritis • Activity • Serum calprotectin • Erosive course • Prognostic factor

Introduction

Juvenile Arthritis (JA) is a chronic childhood inflammatory autoimmune joint disease [1]. Juvenile Arthritis (JA, JIA) comprises a group of heterogeneous forms of arthritis characterized by unknown cause persistent joint inflammatory lasting longer than 6 weeks. Typical classic forms of JIA (systemic, oligo, poly, psoria, enthesopathy) are well known [2]. Some laboratory tests neither rule in nor rule out disease. An elevated ANA titer is not a diagnostic criterion for JA. Erythrocyte sedimentation rate can be normal despite marked involvement of arthritis [3,4]. Pediatric rheumatologists use clinical diagnostic ILAR criteria to confirmed juvenile arthritis [5]. Some researchers reported in their publication that the serum level of calprotectin (S100A8/A9 or MIF related protein 8/14) was correlated with arthritis activity.

The aim of this study

Was to estimate value serum calprotectin in activity of JIA.

Materials and Methods

We evaluated the level of serum calprotectin in 70 children with JIA and 20 adolescents with non-rheumatic joint pain. All 70 children fulfilled the ILAR criteria for JIA, 23 of them had oligoarticular disease subtype (oJA, mean age 7, 2 ± 2,2 years; 17–active, 6–inactive), 22–polyarthritis (pJA, mean age 9 ± 2,3 years; 15–active, 7–inactive), 25–enthesitis related arthritis (erJA, mean age 13 ± 2,7 years; 18–active, 7–inactive). Clinical and radiology data were assessed. *Levels of* serum Calprotectin (sCal), vimentin, Interleukin-6 (sIL6) and Tumor Necrosis Factor (sTNF) were collected and evaluated in all 90 children. This study was carried out at the rheumatology department of H.Turner national medical research center for children's orthopedics and trauma surgery.

Achievement of inactive disease and clinical remission of JA were evaluated according to Wallace criteria. Assessment of X-ray changes in juvenile arthritis was performed using a modified scoring method by Stein rocker. Disease activity range was evaluated by Juvenile Arthritis Disease Activity Score (JADAS27-ESR). Digital data were statistically processed using a software package Microsoft Excel and Statistica 6.0. Quantitative indicators distribution is given as a median (5^{th}; 95^{th} percentile). To determine the significance of differences between the groups we used nonparametric dispersion analysis (ANOVA) by Kruska–Wallis test (for independent groups) Wilcoxon criterion (for dependent groups). The correlation between the parameters under study was analyzed using spearman rank correlation analysis (r). In all statistical analysis procedures p=0.05 was taken for a critical significance level of null statistical hypothesis.

Immunological research was carried out in the laboratory of H.Turner national medical research center for children's orthopedics and trauma surgery. The serum concentration of tumor necrosis factor alpha/sTNF-α was determined using enzyme linked immunosorbent assay (*Elisa-TNF*-alfa; Vector-Best, Russia). The serum concentration of interleukin 6/sIL6 were determined by Electrochemiluminescence Immunoassay (ECLIA) method on Cobas E411 (Roche, Switzerland). The serum concentration of calprotectin/sCal were determined by enzyme linked immunosorbent assay (MIF related protein 8/14 ELISA; Buhlmann laboratories AG/Basel, Switzerland).

Results

Level of sCal in active oJA were 2,61 μg/ml (1,015; 3,935), inactive oJA-1,258 μg/ml (0,772; 2,254), active pJA-5,845 μg/ml (3,408; 8,005), inactive pJA-1,36 μg/ml (0,678; 2342), active erJA-2,98 μg/ml (0,897; 6,876), inactive erJA-0,94 μg/ml (0,429;

1,92); sCal level in children with non-rheumatic joint pain 1,288 µg/ml (0,513; 2,364). All children with active JIA were divided into three groups based on their treatment and aggressive disease. 1st group consist of 12 children with non-erosive JA treated by methotrexate (all erJA, JADAS27-ESR 3.2–4.6), 2nd group–16 children with erosive JA which treated by methotrexate (4 erJA/10 oJA/2 pJA, JADAS27-ESR 4.8–8.2), 3rd group-22 children with erosive JA which switched to anti-TNF drugs (2 erJA/7 oJA/13 pJA, JADAS27-ESR >13). In the 1st group sCal level were 1,0175 µg/ml (0,45; 2,378), sIL6-2,94 pg/ml (1,549; 5,617), vimentin-9,872 U/ml (3,87; 18,81), sTNF-1,144 pg/ml (0,397; 3,757). In the 2nd sCal level were 3,81 µg/ml (2,48; 5,992), sIL6 16,15 pg/ml (1,769; 48,85), vimentin-13,632 U/ml (2,319; 44,492), TNF-1,18 pg/ml (0,204; 3,54). In the 3rd sCal level were 4,828 µg/ml (2,93; 7,954), sIL6-11,048 pg/ml (1,5; 33,7), vimentin-17,22 U/ml (4,212; 52,1), TNF-10,5 pg/ml (0,5; 50,43). Statistical analysis were revealed a correlation between sCalc and active erosive JA (R^2=0.4159, T=4.336, OR erosive JA=3.3193 (predictor factor), 95% CI 1,7006-6,4789, p=0.0079). Serum level of vimentin, IL6 and TNF-alpha were not correlated with risk of erosive course JA (Table 1). The ROC analysis of the sCalc showed that a cut off point more of 2,9 µg/ml may be high prognostic factor for related erosive JA (AUC 0,837 ± 0,0553, 95%CI 0,711-0.923 (Table 2 and Figure 1).

Table 1. Poisson regression modeling of aggressive erosive course of JA in children.

Parameters	Odds ratio	95%CI	Coefficient	Standard error	P-value
Calprotectin	33,193	1,7006 to 6,4789	119,975	0,34122	p=0,0004
Vimentin	10,922	0,9979 to 1,1953	0,088151	0,046045	p=0,0556
Interleukin-6	10,036	0,9371 to 1,0747	0,035678	0,034944	p=0,5104
Tumor necrosis factor alpha	10,342	0,9356 to 1,1433	0,033664	0,051143	p=0,0726

Table 2. ROC analysis of laboratory predictors for aggressive erosive course of JA.

Parameters	AUC	Standard error	95%CI
Calprotectin	0,837	0,0553	0,711 to 0,923
Vimentin	0,545	0,0806	0,404 to 0,681
Interleukin-6	0,689	0,0743	0,548 to 0,808
Tumor necrosis factor alpha	0,627	0,0773	0,485 to 0,755

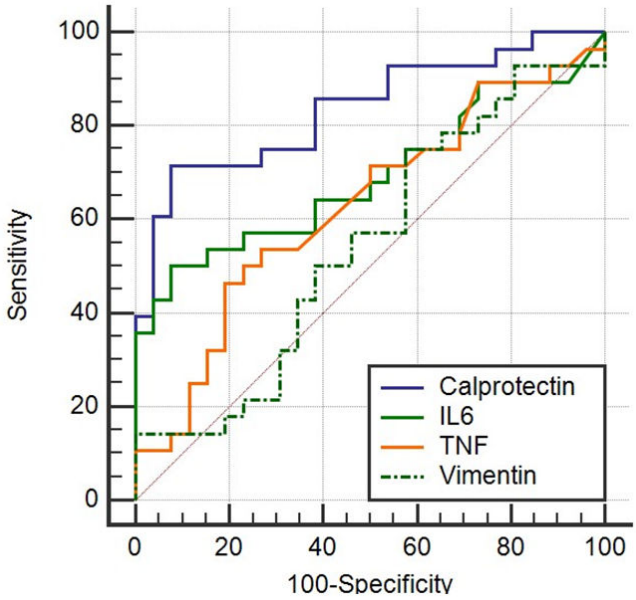

Figure 1. ROC curves of calprotectin, IL6, TNF-alpha and vimentin for predicting aggressive erosive course of juvenile arthritis.

Discussion

We did our research to find possible laboratory tests indicated of early aggressive JA. To meet the objectives of the study, the approach to diagnosis and management JIA in one medical center was used. According to national (Russian) clinical guidelines the degree of aboratory activity is lassessed by the level of CRP and ESR [6]. Only titer of ANF (Antinuclear Factor) and vimentin may be use for estimated value of aggressive JIA. Calprotectin doesn't appear in guidelines for JIA [7].

Calprotectin (MPR 8/14 and S100A8/A9) is a calcium and zinc binding protein that belongs to the S100 family (total molecular weight of 36.5 kDa). Calprotectin present in large quantities of neutrophil granulocytes, less in activated monocytes and macrophages [8]. This protein plays a major role inflammatory reaction and is considered to be a positive acute phase protein. Calprotectin is released following granulation of neutrophil granulocytes during interaction cells with inflammatory activated endothelium. It implicated in the innate immune response as a damage associated molecular pattern protein [9].

Most multicenter studies have demonstrated correlated serum level of calprotectin with activity JIA. The level of calprotectin can reflects the degree of inflammatory activity of JA. Some studies revealed that serum calprotectin levels in patients with active systemic JIA were higher than active in non-systemic JIA. However, not all researchers agree that calprotectin may be predicting factor of flares in JIA. Also correlation between ultrasound dates and concentration of sCalc needs clarification [10-12].

Our results weren't showed substantially higher serum calprotectin levels in children with active JA compared to data in inactive disease and non-inflammatory arthropathy. However, despite the lack of differences, research revealed that serum calprotectin were higher in children with active erosive course of JA. It is known, that early erosive changes in children with non-systemic JIA define like marker of aggressive course. The present study was sent to find correlation between serum level calprotectin and aggressive value of JA. Out study

showed that calprotectin more sensitive laboratory marker of the aggressive course of non-systemic JA.

Conclusion

One of the currently unresolved problems in pediatric rheumatology is identification of markers of aggressive course of JA. Serum calprotectin can serve as one of these markers. Studies confirm that the serum levels of calprotectin are significantly associated with JA disease activity. Our results suggest that calprotectin might be superior to serum IL6 and TNF alpha for erosive course of JA.

Conflict of Interests

Not declared.

Financing Source

Not specified.

Ethical Expertise

The study was approved by the local ethics committee at H.Turner national medical research center for children's orthopedics and trauma surgery (Protocol No. 1 dated 01.20.2014).

References

1. Ravelli, A., & Martini, A.,. Juvenile idiopathic arthritis. *Lancet*. 369.9563 (2007):767-78.
2. Ringold, S., et al. American College of Rheumatology/Arthritis Foundation Guideline for the Screening, Monitoring, and Treatment of Juvenile Idiopathic Arthritis-Associated Uveitis. *Arthritis Care Res.* 71 (2019): 703-716.
3. Kim Y.D., et al. Differential diagnosis of juvenile idiopathic arthritis. *J Rheum Dis*. 24 (2017):131-137.
4. Petty, R.E., et al. International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol*. 31 (2004): 390-392.
5. Baranov, A.A., et al. Management protocol for patients with juvenile arthritis (in Russian). *Current Pediatrics*. 12 (2013):37-56.
6. Mahmud S.A., & Binstadt B.A,. Autoantibodies in the Pathogenesis, Diagnosis, and Prognosis of Juvenile Idiopathic Arthritis. *Front Immunol*. 9(2019):3168.
7. Vaos, G., et al. The role of calprotectin in pediatric disease. *Biomed Res Int*. 2013 (2013):542363.
8. Pathirana, W.G.W., et al. Faecal Calprotectin. *Clin Biochem Rev*. 39 (2018):77-90.
9. Marushko, T., et al. Evaluation of serum calprotectin (MRP-8/MRP-14) levels in patients with juvenile idiopathic arthritis. *J Pediatr Neonat Individual Med*. 10.1 (2021); 100140.
10. Altobelli E., et al. Serum Calprotectin a Potential Biomarker in Juvenile Idiopathic Arthritis: A Meta-Analysis. *J Clin Med*. 10.21 (2021): 4861.
11. Boyko, Y., et al. Blood calprotectin in children with juvenile idiopathic arthritis: relationship to flare development after discontinuation of treatment. *Reumatologia*. 58 (2020):202-207.
12. Hurnakova, J., et al. Serum calprotectin (S100A8/9): An independent predictor of ultrasound synovitis in patients with rheumatoid arthritis. *Arthritis Res Ther*. 17.1 (2015): 1-6.

Cite this article: Kozhevnikov AN, et al. "Serum Calprotectin like a Potential Serum Biomarker of Aggressive Erosive Course of Juvenile Arthritis". J Arthritis, 2022, 11(2), 1-.3.