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Original Article

Evaluation of 14-3-3eta protein as a diagnostic biomarker in the initial assessment of inflammatory arthritis

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Objective: Serum 14-3-3eta are novel biomarkers of rheumatoid arthritis (RA). It is not clear whether 14-3-3eta may be present in other forms of inflammatory arthritis (IA). We evaluated the presence of 14-3-3eta as a diagnostic biomarker in the evaluation IA.

Methods: A retrospective cohort study of adult patients who were evaluated for IA by a rheumatologist with a result for the lab test of 14-3-3eta was conducted.

Results: Of 280 included patients, 30% were diagnosed with RA, 11% with psoriatic arthritis (PsA), and 59% with another condition. Twenty-four (9%) patients had positive results for 14-3-3eta. Fifty-two percent of positive patients were diagnosed with RA, with 48% having another diagnosis including axial spondyloarthritis, gout, Sjögren's, undifferentiated IA, diabetic cheiroarthropathy, prostate cancer with bone metastasis, osteoarthritis, unspecified arthralgia. No patients with PsA had a positive value. RA patients had a higher value for 14-3-3eta compared to non-RA (5.44 [1.56~9.31] vs. 0.69 [0.40~0.98] ng/mL, p=0.03, square brackets are 95% confidence interval values). The mean value for the 14-3-3eta in seropositive RA trended higher than seronegative (8.0 [2.3~13.7] vs. 1.4 [0.4~2.4] ng/mL, p=0.06). In the RA cohort, elevated 14-3-3eta was associated with elevated erythrocyte sedimentation rate (odd ratio=6.62 [1.24~47.09], p<0.04), but not other variables.

Conclusion: 14-3-3eta may aid as a diagnostic biomarker of RA. However, it is not specific for RA, especially at low positive levels, and may be positive in other forms of IA. Ideal cutoff values need to be established for RA and non-RA conditions. It was not found in PsA.

Keywords: 14-3-3eta proteins, Biomarkers, Rheumatoid arthritis, Psoriatic arthritis, Inflammatory arthritis

INTRODUCTION

Identification of new diagnostic biomarkers of inflammatory arthritis (IA), especially seronegative conditions, is of clinical importance. In rheumatoid arthritis (RA), rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) aid in diagnosis of seropositive disease. However, biomarkers may be negative on presentation in up to half of patients and remain negative in approximately 20% of patients [1,2]. While classification criteria exist for research homogeneity, there are no specific diagnostic criteria [3]. Diagnosing seronegative disease is still challenging. Other IA syndromes, such axial spondyloarthritis or psoriatic arthritis (PsA), lack definitive clinical biomarkers. Rheumatologists rely on history, joint counts of tenderness and swelling, and assessments of systemic inflammation, such as elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP),

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along with imaging.

The 14-3-3 proteins are a family of seven isoforms that act as intracellular chaperones. In particular, 14-3-3eta is a synovial-derived proinflammatory isoform that may be elevated in serum of patients with RA [4-6]. Adding 14-3-3eta to the standard RF and anti-CCP serologic work-up may increase sensitivity of diagnosing RA to over 90% [7]. In addition, serial changes in the 14-3-3eta protein levels may predict response to treatment [8]. The positivity of 14-3-3eta in non-RA IA is not well described. The 14-3-3eta protein may not be routinely checked during the initial evaluation for IA, making it difficult to determine its utility as a diagnostic biomarker for non-RA conditions. A detailed real-world clinical experience regarding its use in the initial evaluation of IA has not been described. Thus, we aimed to look at the diagnostic utility of 14-3-3eta protein in patients being evaluated by a rheumatologist for IA.

MATERIALS AND METHODS

Patient and study design

A retrospective Rochester Regional Health electronic chart review of patients being referred to a rheumatologist for evaluation of possible IA with subsequent testing for the 14-3-3eta protein was performed. Inclusion criteria were age ≥18 years, a result for serum 14-3-3eta protein, and evaluation by a rheumatologist from March 2020 to February 2023. Exclusion criteria were age <18 years old or no result for 14-3-3eta protein. The study was conducted under standards of the Helsinki Declaration of 2013. Informed written consent requirement was waived. The Institutional Review Board (IRB) of Rochester Regional Health approved the study (IRB no. 3018 A).

Data collection and diagnoses

The 14-3-3eta protein was measured using Quest Diagnostics Laboratories (Quest Diagnostics Nichols Institute, San Juan Capistrano, CA, USA) with a positive value defined as ≥0.2 ng/mL. All other variables, including demographic and laboratory values, were obtained from the medical chart.

Diagnoses were made through the clinical discretion of the evaluating rheumatologist in a real-world fashion. All diagnoses were based on well-established criteria, including the 2010 American College of Rheumatology (ACR) or European Alliance of Associations for Rheumatology (EULAR) Rheumatoid Arthritis criteria [9], Classification of Psoriatic Arthritis (CASPAR) criteria for Psoriatic arthritis [10], 2019 EULAR/ACR Systemic Lupus Erythematosus classification [11], 2023 EULAR classification criteria for hand osteoarthritis [12], among others (Supplement file). If no specific diagnosis was made, the patient was labeled as unspecified arthralgia.

Statistical analysis

Analyses were conducted with R software (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria) [13]. Descriptive statistics were expressed as frequencies and percentages for categorical variables or as mean and 95% confidence intervals (CI) for continuous variables. Pearson's chi-square test or Fischer's exact test was used to evaluate categorical variables. Two sample Student's t-test or Welch's t-test was used to assess the differences between continuous variables. Logistic regression was used to explore the associations with demographic and lab parameters. Statistical significance was defined as $p<0.05$.

RESULTS

Full cohort

Criteria were met in 280 patients. The cohort mean age was 54.5 (95% CI=52.8~56.2) years, with 72% female and 83% Caucasian. The 14-3-3eta protein was positive in 9% (n=24), with the overall mean positive value of 3.26 (95% CI=0.98~5.54) ng/mL.

Overall, 30% were diagnosed with RA, 16% with osteoarthritis, 11% with PsA, 5% with another specific autoimmune connective tissue disease, and 38% were diagnosed with another condition. For autoimmune connective tissue diseases, eight were diagnosed with axial spondyloarthritis, four patients with Sjögren's disease, three patients with systemic lupus erythematosus, two patients with Behçet's disease, two patients with undifferentiated connective tissue disease, one patient with dermatomyositis, one patient with adult-onset Still's disease, one patient with systemic sclerosis. Other conditions included the following: unspecified arthralgia (n=28), undifferentiated IA (n=19), or other musculoskeletal or inflammatory conditions (n=9, two patients with diabetic cheiroarthropathy, two patients with hypermobility arthralgia, two patients with degenerative disc disease, one patient with adhesive capsulitis, one patient with checkpoint inhibitor arthritis, one patient with prostate cancer with bone metastasis), or crystalline arthropathy (n=7, five with gout and two with calcium pyrophosphate deposition disease).

Positive autoantibodies in the cohort included antinuclear

antibody (n=67, 24%), anti-double stranded DNA (n=11, 4%), anti-U1RNP (n=10, 4%), anti-SS-A (n=9, 3%), anti-Sm (n=3, 1%), anti-histone (n=2, <1%), anti-SS-B (n=1, <1%), anti-beta-2 glycoprotein IgM (n=1, <1%), anti-cardiolipin IgM/IgG (n=1, <1%), anti-centromere (n=1, <1%), anti-RNA polymerase III (n=1, <1%), p-ANCA (n=1, <1%). HLA B27 antigen was positive in 14 patients (5%).

Table 1 illustrates characteristics of patients diagnosed with a positive 14-3-3eta protein. For those with a positive 14-3-3eta protein, RA was diagnosed in 52%, with 48% having another diagnosis. For the three patients with autoimmune connective tissue diseases, two had axial spondyloarthritis and 1 had Sjögren's. For the two patients with other musculoskeletal or inflammatory conditions, one had prostate cancer with bone metastasis and one had diabetic cheiroarthropathy. The patient with crystalline arthropathy had gout. RA patients had a higher value for 14-3-3eta compared to non-RA patients (5.44 [95 CI=1.56~9.31] vs. 0.69 [95 CI=0.40~0.98] ng/mL, p=0.03). Positivity for 14-3-3eta was not significantly correlated with the age, sex, joint swelling, joint tenderness, joint erosion, ESR, or CRP.

Table 1. Descriptive characteristics of the patients with positive 14-3-3eta protein

Diagnosis	Number of patient	Age (yr)	Female	Tender joints present	Swollen joints present	Positive 14-3-3eta	Mean 14-3-3eta value (ng/mL)
Rheumatoid arthritis	83	57.6 (53.3~61.9)	59 (71)	79 (95)	66 (80)	13 (16)	5.44 (1.56~9.31)
Osteoarthritis	44	58.8 (53.6~63.9)	35 (80)	43 (98)	3 (7)	1 (2)	0.40 (NA)
Unspecified arthralgia	28	40.9 (34.9~46.8)	19 (68)	23 (89)	3 (11)	1 (4)	0.30 (NA)
Autoimmune connective tissue diseases*	22	49.9 (43.7~56.1)	20 (90)	17 (77)	5 (23)	3 (14)	0.77 (0.18~1.36)
Undifferentiated inflammatory arthritis	19	58.9 (53.7~64.1)	10 (53)	19 (100)	14 (74)	3 (16)	1.07 (0.49~1.65)
Other musculoskeletal or inflammatory conditions†	9	49.1 (40.0~58.2)	5 (56)	9 (100)	2 (22)	2 (22)	0.30 (0.27~0.32)
Crystaline arthropathy‡	7	60.6 (55.3~65.9)	3 (43)	7 (100)	5 (71)	1 (14)	0.80 (NA)

Values are presented as mean (95% confidence intervals) or number (%). NA: not available. *Eight were diagnosed with axial spondyloarthritis, four patients with Sjögren's disease, three patients with systemic lupus erythematosus, two patients with Behçet's disease, two patients with undifferentiated connective tissue disease, one patient with dermatomyositis, one patient with adult-onset Still's disease, one patient with systemic sclerosis. †Two patients with diabetic cheiroarthropathy, two patients with hypermobility arthralgia, two patients with degenerative disc disease, one patient with adhesive capsulitis, one patient with checkpoint inhibitor arthritis, one patient with prostate cancer with bone metastasis. ‡Five patients with gout, two with calcium pyrophosphate deposition disease.

Table 2. Analysis of 14-3-3eta protein positivity in the rheumatoid arthritis subgroup

Variable	14-3-3eta positive	14-3-3eta negative	p-value
Seropositivity status			0.29
Seropositive (RF and/or anti-CCP)	8 (10)	32 (39)	
Seronegative	5 (6)	38 (46)	
Sex			0.87
Female	9 (11)	50 (60)	
Tender joints present	13 (16)	54 (65)	0.18
Swollen joints present	13 (16)	53 (64)	0.15
Elevated sedimentation rate	9 (11)	26 (31)	0.06
Elevated C-reactive protein	5 (6)	22 (27)	0.75
Presence of joint erosion on X-ray	1 (1)	10 (12)	0.52

Values are presented as number (%). RF: rheumatoid factor, CCP: cyclic citrullinated peptide.

Rheumatoid arthritis subgroup

The characteristics of the 83 patients with RA are shown in Tables 1 and 2. 14-3-3eta was positive in 16%. Of those, 10 (77%) had elevated ESR and 7 (54%) had elevated CRP, and one patient was found to have a joint erosion on X-ray. Table 2 compares characteristics of RA patients with and without positivity to 14-3-3eta. The mean value for the 14-3-3eta in seropositive RA trended higher than in seronegative (8.0 [95% CI=2.3~13.7] vs. 1.4 [0.4~2.4] ng/mL, p=0.06). As shown in Table 2, there was a trend (p=0.06) that those with positive 14-3-3eta had elevated ESR more than those who were negative. Logistic regression found an association with elevated ESR and positive 14-3-3eta with odds ratio 6.62 (95% CI=1.24~47.09, p<0.04). No association was found with age, sex, CRP, RF, or anti-CCP.

The 14-3-3eta sensitivity for the diagnosis of RA was 16% (95% CI=8.6%~25.3%), specificity was 94% (95% CI=90.2%~97.2%), positive predictive value was 54% (95% CI=35.6%~71.7%), and negative predictive value was 73% (95% CI=70.7%~74.6%). For seropositive RA only (excluding seronegative RA), 14-3-3eta sensitivity was 20% (95% CI=9.1%~35.7%), specificity was 94% (95% CI=90.2%~97.2%), positive predictive value was 42% (95% CI=23.8%~62.9%), and negative predictive value was 85% (95% CI=83.2%~87.2%). For seronegative RA only (excluding seropositive RA), 14-3-3eta sensitivity was 12% (95% CI=3.9%~25.1%), specificity was 94% (95% CI=90.2%~97.2%), positive predictive value was 31% (95% CI=14.3%~55.4%), and negative predictive value was 83% (95% CI=81.4%~84.6%).

Psoriatic arthritis subgroup

PsA was the second most common IA diagnosis (n=32). However, no patients with PsA had positive values of 14-3-3eta protein.

Other arthritis subgroup

165 patients were diagnosed with another condition other than RA or PsA. Of this group, 11 (7%) patients had a positive 14-3-3eta protein. Table 1 illustrates characteristics of the diagnoses with a positive 14-3-3eta protein. Of note, it was positive in inflammatory conditions including gout and bony metastasis from prostate cancer, as well as in one patient with diabetic cheiroarthropathy. Furthermore, it was positive in one patient with osteoarthritis and one patient with unspecified arthralgia.

DISCUSSION

We describe the use of 14-3-3eta as a diagnostic biomarker in a real-world clinical cohort of patients evaluated for IA. Overall (Table 1), we found the positivity for serum 14-3-3eta to be relatively low, with only 9% of the total cohort being positive. Approximately 54% of positives were diagnosed with RA (Table 2). Of interest, 14-3-3eta was not exclusive to RA and may be elevated in other systemic rheumatologic conditions as well as non-autoimmune hyperinflammatory conditions, including gout and neoplastic bony metastasis (Table 1). The levels of 14-3-3eta in these conditions were considerably lower than in RA.

Prior studies regarding 14-3-3eta have mainly been in RA. Overall, our RA subgroup findings generally align with these studies. The majority of published data emphasize it as a diagnostic biomarker most clinically useful in seronegative RA. A meta-analysis by Wang et al. [6] concluded that 14-3-3eta protein could be used as a complementary biomarker in diagnosis of RA.

Shovman et al. [14] found the prevalence of 14-3-3eta positivity in patients with early RA was 58%. Yarlagadda et al. [15] found a higher positivity rate in both seropositive (78%) and seronegative (71%) groups. Others have suggested that when combined with testing for RF and anti-CCP, it may raise diagnostic sensitivity in RA to 90% [7]. Our overall positively rate was lower than these studies. This may be for a few reasons. One reason may be that our study was not just assessing RA but all patients referred in a real-world fashion for possible IA. Given that testing for 14-3-3eta was left to the discretion of the evaluating rheumatologist, it is likely that not every case of RA over our study time period of 3 years was included in our analysis, which would likely decrease our sensitivity. Additionally, we only analyzed a one-time lab value of 14-3-3eta obtained during initial evaluations for IA, which does not account for the dynamic nature of 14-3-3eta levels with disease activity [8]. Similarly, it is possible that the use of anti-inflammatory medications, such as glucocorticoids, could influence the level, but additional study of this is necessary for confirmation. It is likely that many patients were previously treated with those medications by the referring physician prior to rheumatologist evaluation. Given the real-world nature of the study, we were not able to control for this limitation and future prospective studies could assess this.

There has been suggestion that 14-3-3eta may be positive in erosive PsA [16]. We did not find any positivity in our subgroup

with PsA. Our study was not designed to evaluate 14-3-3eta as a marker of erosion but instead as a diagnostic biomarker. We cannot recommend use of 14-3-3eta as a diagnostic marker for PsA, but further study is necessary to determine if it could be used as a marker of erosive disease progression. Elevated 14-3-3eta in RA patients has been correlated with a radiographic erosive disease, especially when monitored over many months [17,18]. In our study, only one RA patient with positive 14-3-3eta had a joint erosion. Our study is limited by assessing for radiographic evidence of erosive disease only at the time of initial evaluation. Additionally, imaging was left to the discretion of the evaluating rheumatologist, which may decrease sensitivity. A recent study also found that erosive changes are not frequently found during initial RA evaluations [19].

Different cutoffs for positivity have been described for 14-3-3eta, which may relate to differences in the manufacturer of the test. Salman et al. [20] suggested that a higher 14-3-3eta cutoff of ≥0.33 ng/mL was associated with 89% sensitivity and 82% specificity in RA [20]. Alternatively, Guan et al. [7] used a cut off of >1.44 ng/mL with a sensitivity of 79% and specificity of 74%. Other studies used even high cutoffs of 1.89 and 2.60 ng/mL [21,22]. Differences in sensitivity and specificities have been compared in a detailed review [23]. Overall, and in concordance with most prior reports, we noted that in RA the level of 14-3-3eta was significantly higher compared to non-RA. However, given that the literature is varied on what value of 14-3-3eta should be used to describe "positivity" in RA, this would impact sensitivity, specificity, positive predictive value, and negative predictive value. A prior study shares our findings that 14-3-3eta is not exclusive to RA and may be detected in other autoimmune and non-autoimmune inflammatory conditions, but this study is limited by not stating which assay was used for 14-3-3eta detection or what the positivity cutoff value in RA was [22]. A higher cutoff limit would add specificity and positive predictive value for the diagnosis of RA, while lower values would add sensitivity but may increase false positivity. Given that our study illustrates that 14-3-3eta levels at ≥0.2 ng/mL is not exclusive to RA, future study is necessary to determine the ideal cutoff value to optimize diagnostic accuracy in RA as well as in other inflammatory conditions. Alternatively, a range of positivity values, such as weak, moderate, or strong, may be appropriate to aid diagnosis, with the realization that weak positives may be seen in non-RA conditions. Both options would require a large international cohort of RA patients to establish the most accurate values. In addition, others have looked at the sensitivity and specificity of combinations of novel biomarkers in RA, including 14-3-3eta [21]. Overall, combination of positive markers may have the best accuracy for diagnosing RA [21,23].

Our study does have additional limitations. As a retrospective real-world cohort study, our findings were limited by the completeness and accuracy of the electronic medical records and inability to account for potential confounders. Complete joint counts for tenderness or swelling for all patients were not available, and we were limited to describing presence or absence of such. Disease activity assessments were not available for many patients and not included in this study. The majority of our patients were Caucasian (84%). Previous studies looked at cohorts of different ethnicities, and we are unable to comment whether race or ethnicity may play a role in positivity [23]. This would be an interesting area of future study.

CONCLUSION

Overall, 14-3-3eta may aid as a diagnostic biomarker in the evaluation of IA, especially RA, but warrants caution and clinical expertise for interpretation. It is not specific for a particular disease, especially at low positive levels. It does not appear to be a diagnostic biomarker in PsA. Further study is necessary to define the ideal cutoff limit for the test in RA versus other conditions.

SUPPLEMENTARY DATA

Supplementary data can be found with this article online at https://doi.org/10.4078/jrd.2024.0110

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CONFLICT OF INTEREST

Dr. Ocon is a consultant for Amgen, Inc., unrelated to this manuscript. All other authors have no financial or other conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design of study: RS, AJO. Acquisition of data: RS, AM, AAN, AJO. Analysis and/or interpretation of data: RS, AM, AAN, AJO. Drafting the manuscript: RS, AJO. Revising the manuscript critically for important intellectual content: RS, AM, AAN, AJO.

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