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Do we underestimate musculoskeletal ultrasonography in the diagnosis of polymyalgia rheumatica with or without giant cell arteritis?

Polimiyaljia romatika ve dev hücreli arterit tanısında muskuloskeletal ultrasonografi kullanımını azımsıyor muyuz?

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Abstract

Objective: We aimed to determine how often musculoskeletal ultrasonography (MSUS) is used in real-life practice for the evaluation of 2012 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria in polymyalgia rheumatica (PMR) patients with or without giant cell arteritis (GCA).

Methods: All patients have been prospectively registered in the Hacettepe University Vasculitis Research Center database since October 2014. The clinical information, laboratory and MSUS findings of patients registered in database until January 2023 were also retrospectively analyzed from the hospital electronic files and patients' charts. MSUS findings were analyzed following the criteria. Patients were divided into two groups: those with or without GCA. The utility of the 2012 ACR/EULAR provisional PMR classification criteria was compared in two groups.

Results: As of January 2023, 106 patients were included in the analysis. Eighteen patients were excluded from the study due to missing data and the diagnosis changed to inflammatory arthritis during the follow-up period. The mean age at diagnosis of the patients was 66.8 (7.53). Sixty (68.2%) of these patients had solely PMR, while twenty-eight (31.8%) had GCA accompanying PMR. Only 45 (75%) of 60 PMR patients and 12 (42.9%) patients with concomitant GCA diagnoses met the criteria. The criteria were higher solely in PMR patients (p=0.007). MSUS was applied to only 22.7% of patients. We found that only three patients did not meet the criteria if MSUS was not performed, and the rate of meeting the criteria in all patients changed from 64% to 61.3%.

Conclusion: While the 2012 PMR provisional criteria are useful for solely PMR patients, they should be developed for patients with GCA accompanying PMR. In both groups, shoulder and hip ultrasonography

Öz

Amaç: Dev hücreli arteritin (DHA) eşlik ettiği ve izole polimiyalji romatika (PMR) hastalarında 2012 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) sınıflandırma kriterlerinin değerlendirilmesinde kas-iskelet ultrasonografisinin (MSUS) gerçek yaşam pratiğinde ne sıklıkta kullanıldığını belirlemeyi amaçladık.

Yöntem: Tüm hastalar Ekim 2014 tarihinden itibaren tüm hastalar prospektif olarak Hacettepe Üniversitesi Vaskülit Araştırma Merkezi veri tabanına kaydedildi. Ocak 2023 tarihine kadar veri tabanımızda kayıtlı olan hastaların klinik bilgileri, laboratuvar ve MSUS bulguları da hastane elektronik sisteminden ve hasta dosyalarından incelendi. Hastaların ultrasonografi bulguları kriterlere göre analiz edildi. PMR hastaları DHA eşlik eden ve etmeyenler olarak iki gruba ayrıldı. 2012 ACR/EULAR geçici PMR sınıflandırma kriterlerinin karşılama oranı iki grupta karşılaştırıldı.

Bulgular: Ocak 2023 itibariyle 106 hasta analize dahil edildi. PMR kriterlerine ilişkin eksik veriler ve takip süresince tanının enflamatuvar artrit olarak değişmesi nedeniyle 18 hasta çalışma dışı bırakıldı. Bu hastaların 60'ında (%68,2) sadece PMR, 28'inde (%32,8) PMR'ye eşlik eden DHA vardı. Hastaların ortalama tanı yaşı 66,8 (7,53) idi. 60 PMR hastasının sadece 45'i (%75) ve eşlik eden DHA tanısı olan 12 (%42,9) hasta kriterleri karşıladı. Kriterler yalnızca PMR hastalarında daha yüksekti (p=0,007). MSUS hastaların sadece %22,7'sine uygulandı. Hastalara MSUS yapılmasaydı yalnızca üç hasta kriterleri doldurmayacaktı ve tüm hastalarda kriterleri karşılama oranı %64'ten %61,3'e değişecekti.

Sonuç: 2012 PMR geçici kriterleri sadece PMR hastaları için faydalı iken, PMR'ye eşlik eden DHA'lı hastalar için geliştirilmelidir. Anatomik güçlükler ve yetersiz eğitim nedeniyle her iki grupta da omuz ve kalça

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was performed less frequently due to anatomical difficulties and insufficient training. Therefore, clinicians should pay attention to using MSUS and recommended criteria when diagnosing PMR in daily rheumatology practice.

Keywords: Polymyalgia rheumatica, giant cell arteritis, the new 2012 EULAR/ACR PMR provisional classification criteria, musculoskeletal ultrasonography

ultrasonografisi daha az uygulandı. Bu nedenle klinisyenler günlük romatoloji pratiğinde PMR tanısı koyarken MSUS kullanımına ve önerilen kriterlere dikkat etmelidir.

Anahtar Kelimeler: Polimiyaljia romatika, dev hücreli arterit, 2012 ACR/EULAR PMR provizyonel sınıflama kriterleri, muskuloskeletal ultrasonografi

Introduction

Polymyalgia rheumatica (PMR) is an inflammatory disease that generally affects people over 50, characterized by pain and stiffness in the neck-shoulder-hip region, with elevated acute phase reactants and negative autoantibodies. Different sets of criteria have been previously defined for diagnosing or classifying PMR. However, the specificity of these criteria in differentiating PMR from other rheumatic diseases is lower than expected. Therefore, 2012 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) provisional PMR classification criteria were developed using musculoskeletal ultrasonography (MSUS) in 2012.[1,2] As a result, the PMR classification criteria showed optimal sensitivity (92.6%) and specificity (81.5%) in discriminating PMR from inflammatory arthritis and other diseases which can mimic PMR in symptoms.

Furthermore, the specificity of the criteria increased to 91.3% with the addition of the MSUS examination.[3] While MSUS has been added to these criteria, how often they are used in daily practice still needs to be discovered. On the other hand, giant cell arteritis (GCA) is another common inflammatory disease in the elderly population and overlaps with PMR. PMR is related to GCA in 16-21% of cases, and up to 50-90% of GCA cases may have PMR at presentation.[1] Although PMR criteria have been previously studied solely in PMR patients, their sensitivity has not been demonstrated in patients with GCA. In a recent prospective study, the prevalence of GCA in newly diagnosed PMR patients was investigated, and 89% of PMR patients with GCA diagnoses fulfilled those criteria.[4]

We aimed to to determine how often ultrasound is used in real-life practice for evaluation of classification criteria in PMR patients with or without GCA.

Materials and Methods

All patients diagnosed with PMR have been prospectively registered at the Hacettepe University Vasculitis Research Center (HUVAC database) between October 2014 and January 2023. Patients diagnosed with PMR based on an experienced clinician were included. Eighteen patients with insufficient clinical and laboratory information at the time of diagnosis were excluded from the study. Demographic data, clinical characteristics, laboratory findings, and MSUS findings of the patients were recorded. The clinical information and laboratory findings of the patients registered in our database until January 2023 were also retrospectively analyzed from the hospital electronic files and patients' charts.

Laboratory data including erythrocyte sedimentation rate (ESR) (mm/h), C-reactive protein (CRP) (mg/dL), complete blood count, rheumatoid factor (RF; positive if >20 IU/mL), and anticitrullinated peptide antibody (ACPA; positive if >5 IU/mL) levels were recorded. The criteria were studied for patients who met the criteria required for the 2012 ACR/EULAR criteria to be applied (Table 1). Morning stiffness and duration, hip pain or range of motion, absence of RF/ACPA, absence of other joint involvement at baseline were documented. If the patient did not use USG, getting 4 points from these criteria would fulfill the criteria.

US Examination

MSUS was performed by experienced rheumatologists trained in ultrasound. Parameters of the MSUS were included according to criteria: Both shoulders with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis (1 point), at least one shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least one hip with synovitis and/or trochanteric bursitis (1 point).[2] If MSUS was done, 5 points were required to fulfill the criteria (Table 1).

PMR patients with GCA met the 1990 ACR criteria for GCA. In addition, they had a positive temporal artery biopsy/temporal artery ultrasonography or evidence of large vessel vasculitis at fluorodeoxyglucose-positron emission tomography/computerized tomography scan.[5] We divided the patients into two groups: Those solely with PMR and those with a concomitant GCA diagnosis. We analyzed the sensitivity of those criteria in diagnosing patients with solely PMR and patients with PMR and GCA concomitantly. Hacettepe University Ethics Commission has approved this study (GO 21/198).

Table 1. 2012 American College of Rheumatology/European League Against Rheumatism provisional criteria for the classification of polymyalgia rheumatica[2]

	Point without US (0-6)*	Point with US (0-8)*
Morning stiffness duration >45 min	2	2
Hip pain or limited range of motion	1	1
Absence of RF or ACPA	2	2
Absence of other joint involvement	1	1
At least one shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least one hip with synovitis and/or trochanteric bursitis	-	1
Both shoulders with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis	-	1

*A score of 4 or more is categorised as PMR in the algorithm without US and a score of 5 or more is categorised as PMR in the algorithm with US

ACPA: Anticitrullinated protein antibody, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, PMR: Polymyalgia rheumatica, RF: Rheumatoid factor, US: Ultrasound

Statistical Analysis

Statistical analysis was performed using SPSS version 25. Continuous data were described as median [interquartile range (IQR)] or mean [standard deviation (SD)], and categorical variables as percentages. The differences between two groups were investigated using the Mann-Whitney U and Student's t-test. The categorical variable was interpreted using the chi-square tests. The level of significance was chosen to be $p<0.05$.

Results

Patients Clinical Characteristics

We detected 106 patients with PMR, fourteen patients were excluded due to missing data and four patients due to an inflammatory arthritis diagnosis (3 of them elderly onset rheumatoid arthritis, one spondylarthritis) during the follow-up. The final analysis included 88 [n=60 (68.2%) female] patients. There were 60 patients in the PMR only group (68.2%). The prevalence of patients with both PMR and GCA diagnoses was 31.8%. PMR with GCA patients had a longer disease duration than the PMR only group (p=0.007).

All patients were older than 50 years and had elevated acute-phase reactants. The mean (± SD) age at diagnosis of PMR was 66.8 (±7.53) years. Characteristic features of the patients are shown in Table 2. The laboratory parameters at the time of diagnosis were as follows: Mean (± SD) ESR was 58.1 (±28.7) mm/h, median (IQR) CRP was 3.72 (1.1-23.2) mg/dL, mean (± SD) hemoglobin was 12.4 (±1.5) g/dL, and mean (SD) platelet count was 303,000 (±148,000)/mL. MSUS was performed in only 20 (22.7%) patients; 17 were PMR solely patients, and 3 were PMR with GCA patients. In MSUS examination, eight (40%) patients had bilateral shoulder MSUS findings in the examined regions; Biceps tenosynovitis subdeltoid bursitis or glenohumeral synovitis. In addition, 7 (35%) patients had unilateral inflamed shoulder findings with hip synovitis and/or trochanteric bursitis. MSUS examination of five patients (25%) was normal.

Applicability of Classification Criteria for Both Groups

A total of 57 (64.7%) patients met the 2012 ACR/EULAR provisional PMR classification criteria. While of the 60 patients with solely PMR, 45 (75%) met the criteria, only 12 (42.9%) of the 28 PMR with GCA patients met the criteria. Disease duration was longer in PMR with GCA patients (p=0.007). The rate of fulfilling the criteria in solely PMR patients was significantly higher than in PMR with GCA patients (Table 3). While almost all patients within the isolated PMR patients had morning stiffness, half of

Table 2. Characteristic features of all PMR patients

Age at the diagnosis, years*	66.8 (±7.53)
Disease duration, years**	3.54 (0.18-14.7)
PMR with GCA patients, n (%)	28 (31.8)
Constitutional symptoms (n=82)	67 (81.7)
Morning stiffness ≥45 min (n=73)	67 (91.7)
Hip pain or limited range of motion (n=74)	66 (89.1)
Absence of RF and/or ACPA (n=76)	65 (85.5)
Absence of other joint involvement (=51)	46 (90.1)
ESR (mm/h)*	58.1 (±28.7)
CRP (mg/dL)**	3.72 (1.1-23.2)
Leucocyte (x10^3/mm^3)	10.3 (±2.8)
Hemoglobin (gr/dL)*	12.4 (±1.5)
Platelets (x10^3/mm^3)*	303 (±148)
RF positivity (>20 IU/mL), n (%)	6 (7.1)
ACPA pozitivity, n (%), n=84	4 (4.7)
RF or ACPA positivity, n (%)	7 (8.35)

*ACPA: anti-cyclic citrullinated peptide antibody, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, GCA: Giant cell arthritis, MSUS: Musculoskeletal ultrasonography, PMR: Polymyalgia rheumatica, RF: rheumatoid factor, *mean (±standard deviation), **Median (IQR)*

Table 3. Comparison patients with solely PMR and PMR with GCA patients

	Patients swith solely PMR (n=60)	PMR with GCA patients (n=28)	p
Age at diagnosis, years, mean (± SD)	65.9 (8)	68.7 (6.0)	0.13
Sex (female), n (%)	40 (66.7)	20 (71.4)	0.42
Disease duration, years, median (min-max)	**3.4 (0.18-10.5)**	**5.5 (0.2-14.7)**	**0.007**
Morning stiffness ≥45 min, n (%)	**54 (96.4)**	**13 (76.5)**	**0.02**
Hip pain or limited range of motion (n=63), n (%)	52 (91.2)	14 (82.4)	0.2
Absence of RF/ACPA, n (%)	47 (88.7)	18 (78.3)	0.25
Absence of other joint involvement, n (%)	35 (89.7)	11 (91.7)	0.6
The patients for fulfilled of score 4 and more n, (%)	**45 (75)**	**12 (42.9)**	**0.004**
MSUS, n (%) • Normal • Both shoulders inflamed* • At least one shoulder and at least one hip inflamed**	15 (25) 4 (6.6) 6 (10) 5 (8.3)	5 (17.8) 1 (3.5) 2 (7.1) 2 (7.1)	0.3

**Both shoulders with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis, **At least one shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis and at least one hip with synovitis and/or trochanteric bursitis, ACPA: Anticitrullinated protein antibodies, GCA: Giant cell arteritis, MSUS: Musculoskeletal ultrasonography, RF: Rheumatoid factor, PMR: Polymyalgia rheumatica, SD: Standard deviation*

PMR with GCA patients had morning stiffness. There was no difference between the groups regarding other criteria. In PMR patients with GCA, a lower rate of MSUS was performed. MSUS was performed on only 20 patients. Even if MSUS was not performed in 17 of these patients, it was observed that they filled the criteria. We found that only three patients did not meet the criteria if MSUS was not performed, and the rate of meeting the criteria in all patients changed from 64% to 61.3%.

Discussion

In this present study, we performed the 2012 EULAR/ACR provisional classification criteria in our PMR and GCA cohort. Our data showed that these criteria are not used adequately in PMR with GCA patients. Even though criteria have been developed to diagnose PMR, the clinician's experience is still important for the diagnosis of those patients. Our results showed that MSUS did not significantly alter the sensitivity of the criteria. Although MSUS is part of the criteria, it was used less frequently in the diagnosis of the disease for some valid reason.

Until 2012, Bird[5] and Hailey's[6] criteria were used to diagnose PMR. Macchioni et al.[7] showed that Bird[5] and Healey's[6] criteria were insufficient to distinguish between inflammatory rheumatic diseases such as RA and PMR from each other. Because of these reasons, 2012 ACR/EULAR provisional PMR classification criteria set was developed in 2012.[2] After the 2012 provisional PMR criteria were developed, their performance was evaluated in previous studies, but there has yet to be a new update on the provisional PMR criteria.[7,8] However, the efficiency of these criteria has yet to be evaluated in PMR with GCA patients. It has yet to be compared regarding efficiency in PMR patients solely and PMR with GCA patients.

In our present study, the ACR/EULAR criteria frequency was 64.7% in all PMR patients; this ratio was lower compared to other studies. Especially in PMR with GCA patients, we noticed that patients previously diagnosed with GCA and had pain in the shoulder and hip girdle was followed up with the diagnosis of PMR, even if they did not meet the 2012 criteria. The sensitivity of the criteria was 42% in patients with GCA. In a Korean cohort study involving 98 patients with PMR, they found that 80 (81.6%) patients achieved ≥4 points, and particularly 26 patients (26.5%) achieved 6 points. Besides, the most common finding in their study was hip pain or restricted range of motion (84.7%), while the least seen symptom was morning stiffness for more than 45 minutes (54.1%). Our data showed that the percentage of all criteria was similar (morning stiffness: 96.1%, hip pain or restricted range of motion: 91.2%).[8,9]

In a Japanese PMR cohort, the rate of patients fulfilling the criteria was less than in our cohort (42% vs. 75%). While almost all patients in our PMR cohort had morning stiffness, one in five patients in the Japanese PMR cohort had morning stiffness. For this reason, our rate of meeting the criteria may have been higher than theirs.[10] Macchioni et al.[7] reported that morning stiffness was 91%, similar to our cohort. However, our PMR with GCA patients' morning stiffness duration was 76.5%. The difference in filling those criteria between these studies may have been due to racial differences and hospital registry systems.

Morning stiffness and absence of RF/ACPA positivity had a higher score than others in the criteria set. In particular, RF positivity is a score that increases with age, and it can be found positive in 10 percent of individuals.[11] In our cohort, 7 (8.3%) patients had RF or ACPA positivity. However, only two of them met the criteria. Considering that PMR and GCA can be seen in the elderly, it is possible to detect age-

related RF positivity in those patients. Therefore, it may be helpful to reconsider the score given to RF positivity.

When we look at the criteria items in detail, morning stiffness was higher in patients with solely PMR than the PMR with GCA patients ($p<0.02$). Other criteria domains were similar. As a result, patients with solely PMR diagnosis met the criteria at a higher rate than the PMR with GCA patients in our cohort. When we look at the literature, there was another study in which morning stiffness was less common in patients with GCA, although it was not statistically significant. Again in this study, the usefulness of the criteria between groups was similar.[4]

Our study evaluated 20 patients (22.7%) with MSUS. After implementing MSUS into the classification criteria guideline, the total score ≥5 had increased to a sensitivity of 66% and specificity of 81%, differentiating it from other inflammatory rheumatic diseases.[2,12] However, there are conflicting results in the literature regarding the sensitivity and specificity of these criteria. Macchioni et al.[7] emphasized that adding the US to the criteria increased the specificity. In contrast, in another study, the sensitivity increased when the US was added to the criteria, and the specificity decreased.[3] Although MSUS was performed in a few patients in our study, the sensitivity did not change significantly when we excluded the US findings from the criteria. In a retrospective study conducted on 98 PMR patients, the sensitivity of the criteria was 81.6% without using the US. In our PMR cohort, the sensitivity of the criteria was 61.3% without using the US.[9] The findings in our study show that US does not contribute to the sensitivity of the criteria. In the study of Burg et al.[4], the sensitivity of the criteria was 89% in PMR-GCA patients.[4] On the other hand, in our study, it was found to be 42.9%. The other study was prospective, with no missing data, and US was performed on all patients. This may be the reason why our results are different.

Although recommended, there may be some valid reasons for the insufficiency of MSUS in the diagnosis:

1. Application of shoulder and hip sonograhpy is more difficult due to the anatomy of those joint regions and inexperience of many clinicians in handling it.

2. Some of these patients may have undergone MSUS, but there was no any recorded report of their sonographies.

3. There could be less emphasis on shoulder and hip ultrasonography education during the rheumatology fellowship education.

Study Limitations

Our present study has several limitations. Firstly, our study was performed at a single tertiary referral center. For this reason, more patients with a pre-diagnosis of GCA may be referred to us, and therefore the frequency of GCA may be higher, which may be a potential bias/limitation. Secondly, although this is a prospectively recorded database, only some criteria could be evaluated because information on every patient in the database could not be reached. On the other hand, only some patients underwent MSUS, so it is difficult to determine how much the US contributes to the criteria.

Conclusion

Our study demonstrated the usefulness of PMR classification criteria in rheumatology. These results suggest that MSUS should be included explicitly in the diagnostic process. It seems important for clinicians to make MSUS a part of rheumatology education. Clinician experience is still one step ahead in diagnosing PMR. The differential diagnosis of inflammatory arthritis should be made quite well. Therefore, when diagnosing PMR patients, clinicians should consider all criteria and the use of MSUS in their daily clinical practice.

Ethics

Ethics Committee Approval: Hacettepe University Ethics Commission has approved this study (GO 21/198).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: G.S.U., G.K.Y., K.M., L.K., Ş.A.B., S.K., İ.E., Ö.K., Design: G.S.U., G.K.Y., K.M., L.K., Ş.A.B., S.K., İ.E., Ö.K., Data Collection or Processing: G.S.U., G.K.Y., K.M., L.K., Ş.A.B., S.K., İ.E., Ö.K., Analysis or Interpretation: G.S.U., G.K.Y., K.M., L.K., Ş.A.B., S.K., İ.E., Ö.K., Literature Search: G.S.U., G.K.Y., K.M., L.K., Ş.A.B., S.K., İ.E., Ö.K., Writing: G.S.U., G.K.Y., K.M., L.K., Ş.A.B., S.K., İ.E., Ö.K.

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