Ultrasound shoulder assessment of calcium pyrophosphate disease with suspected polymyalgia rheumatic

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Abstract

Objective

Polymyalgia rheumatica (PMR) is characterised by inflammatory pain of shoulders and the pelvic girdle that affects older people. Conditions that can mimic PMR include rheumatoid arthritis (RA), spondyloarthritis (SpA) and calcium pyrophosphate disease (CPPD). In this study, we aimed to define the prevalence of CPPD among patients with polymyalgic syndrome with suspected PMR according to recent ACR/EULAR criteria.

Methods

This was an observational study in which we included patients with polymyalgic syndrome (inflammatory pain of shoulders, elevated C-reactive protein (CRP) level, and age >50 years). All patients were tested for RA antibodies and underwent ultrasonography (US) of shoulders [gleno-humeral effusion, biceps tenosynovitis, sub-acromiodeltoid (SAD) bursitis, synovitis and CPPD of the acromio-clavicular (AC) joint and humeral bone erosion].

Results

We included 94 patients with polymyalgic syndrome (mean age 69.4±11.3 years, 67% female); 27 had a diagnosis of RA and 14 SpA. The remaining 52 were considered to have PMR according to ACR/EULAR criteria for PMR; 25 had a diagnosis of CPPD. As compared with PMR patients without CPPD, those with CPPD more frequently had humeral bone erosion (p=0.003), synovitis and CPPD of the AC joint (p<0.0001 for both) and less frequently SAD bursitis (p=0.0098). For PMR diagnosis, the most sensitive US features were SAD bursitis (96.3%) and biceps tenosynovitis (85.2%), despite low specificity. For CPPD diagnosis, CPPD of the AC joint had the best ratio of sensitivity to specificity (sensitivity: 85.2%; specificity: 97.1%).

Conclusion

Detection of CPPD is relatively frequent with suspected PMR. Adding US assessment of the AC joint to usual US screening might help the clinician better distinguish PMR from other conditions, notably CPPD.

Key words

ultrasound, polymyalgia rheumatica, shoulder, chondrocalcinosis

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Received on November 15, 2019; accepted in revised form on January 20, 2020.

Competing interests: none declared.

Introduction

Polymyalgia rheumatica (PMR) is characterised by inflammatory pain and morning stiffness affecting shoulders and the pelvic girdle (1). It occurs in people over age 50. Among this population, PMR is the most common inflammatory rheumatic disease of older people, but many conditions can mimic PMR, such as rheumatoid arthritis (RA), late-onset spondyloarthritis, calcium pyrophosphate disease (CPPD) or endocrine disorders (2). Moreover, many of these disorders respond to initial steroids therapy. Overdiagnosis of PMR can lead to unnecessary prolonged use of steroids. After long-term follow-up, 5% to 23% of patients had a diagnostic shift (3-5). The lack of a gold standard diagnostic test and the moderate specificity of usual diagnostic criteria could explain this overdiagnosis of PMR.

Because it has been suggested that ultrasonography (US) is useful in the diagnosis of PMR (6, 7), recent American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) guidelines for PMR diagnosis recommend US to increase the diagnostic accuracy (8). With the new criteria, the presence of an RA immunologic test [rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPA)] decreases the diagnosis score, whereas US features of PMR (biceps tenosynovitis, gleno-humeral (GH) or hip synovitis, trochanteric or subdeltoid bursitis) increases it. However, the diagnostic use of these criteria was not evaluated for the presence of CPPD.

In this study, we aimed to define the prevalence of CPPD among patients with polymyalgic syndrome with suspected PMR according to recent ACR/EULAR criteria.

Patients and methods

Patients and study design

In this observational study, inclusion criteria were polymyalgia syndrome characterised by morning stiffness more than 45 min of shoulders, elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level, and age >50 years. All patients underwent a clinical exam, blood tests and US of shoulders to assess the potential differential diagnosis. Patients were tested for RA antibodies (RF and ACPA). With pain and positive RA antibodies, the diagnosis was RA (2010 ACR/EULAR criteria [9]). Spondyloarthritis (SpA) was assessed systematically as a differential diagnosis. Enthesitis, dactylitis, inflammatory back pain, psoriasis, and peripheral arthritis were evaluated for each patient. Patients fulfilling European Spondyloarthropathy Study Group criteria had a final diagnosis of SpA (10). The remaining patients were considered to have PMR according to clinical ACR/EULAR criteria (8). We systematically screened CPPD in all patients by US analysis of AC joints and joint fluid analysis. The CCPD diagnosis was confirmed by the presence of CPP crystals in any synovial, past or present, fluid joint analysis as recommended (11). Exclusion criteria were age <50 years, history of shoulder trauma or surgery and corticosteroids injection within the last 3 months. A control group without shoulder pain also underwent US.

Ethics statement

The Institutional Review Board (IRB No. 12-011) of Paris North Hospitals approved this study. All patients gave their written informed consent to participate.

US assessment

US assessment of bilateral shoulders in all patients was performed by one trained rheumatologist who used an Esaote MyLab70 echograph (linear probe, 7.5 to 15 MHz) with blinding to the diagnosis and clinical data. A standardised scanning method was used (12). For PMR diagnosis, usual US features of PMR were assessed: GH effusion, long-head biceps tendon tenosynovitis and SAD bursitis (Fig. 1A-D). CPPD assessment involved analysis of bone humeral erosions and the AC joint. Thus, for all patients, the following items were systematically investigated by a dichotomous assessment (presence or absence of a given US feature): GH effusion, long-head biceps tendon tenosynovitis, sub-acromial and SAD bursitis, acromio-clavicular (AC) synovitis, humeral

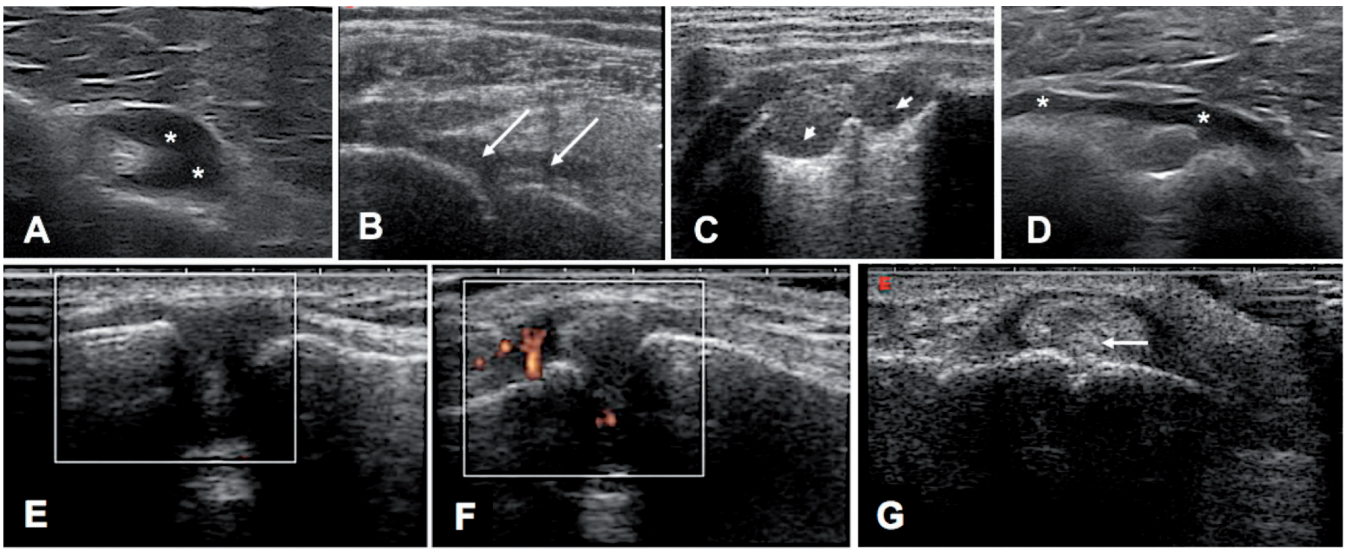

Fig. 1. Ultrasonography assessment of shoulders and acromioclavicular (AC) joints.
A: Biceps tenosynovitis (white asterisk) in axial view. **B**: Gleno-humeral synovitis (white arrow) in a posterior view. **C**: Erosion of humeral bone (white arrowhead). **D**: Sub-acromiodeltoid bursitis (white asterisk). **E**: Normal AC joint. **F**: Synovitis of AC joint with hypervascularisation in power Doppler. **G**: Hyperechoic foci of AC joint corresponding to calcium pyrophosphate disease.

bone erosion and AC chondrocalcinosis. For AC joint scanning, the transducer was oriented in a longitudinal and transversal view (13). As previously reported (14), AC synovitis was defined by the association of the two following items: 1) presence of swelling of the AC joint (joint cavity dome above the external margins of synovial cavity) and 2) hypervascularisation on power Doppler US (Fig. 1F). Because of no previous definition, AC chondrocalcinosis was defined as the presence of hyperechoic foci (calcification) in the AC joint cavity (Fig. 1G).

Statistical analysis

Data are presented as median [interquartile range (IQR)] or mean±SD. Wilcoxon's test was used for quantitative variables and Fisher's exact test for categorical data. Two-sided $p<0.05$ was considered statistically significant.

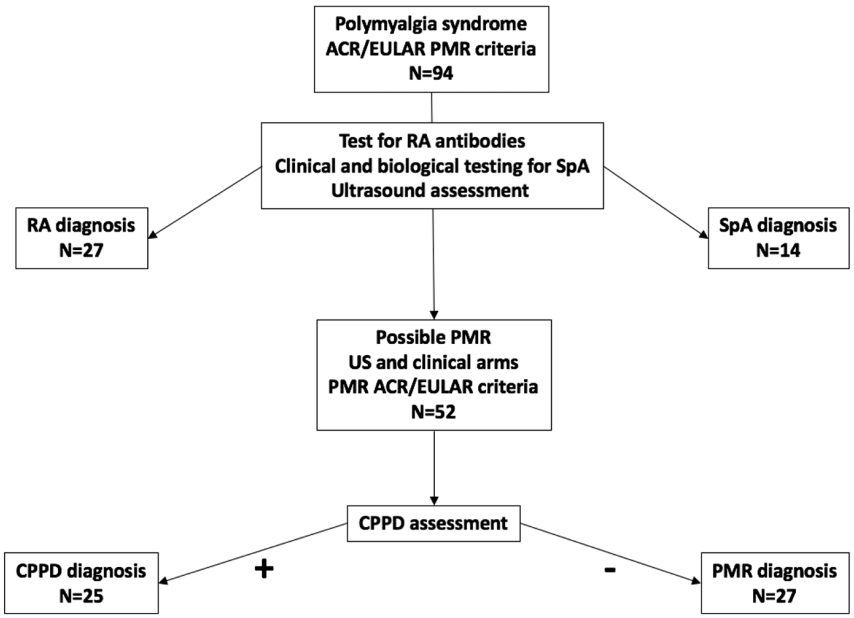

Fig. 2. Flowchart of participants in the study.
ACR/EULAR, American College of Rheumatology/European League Against Rheumatism; PMR, polymyalgia rheumatica; SpA: spondyloarthrits; RA: rheumatoid arthritis; US: ultrasonography; CPPD: calcium pyrophosphate disease.

Results

Baseline characteristics

We included 94 patients (mean age 69.4±11.3 years, 67% female) with polymyalgic syndrome and 23 healthy controls (mean age 63.8±11.6 years, 61% female) without shoulder pain. Among patients, 27 had a diagnosis of RA (mean age 61.3±8.6 years, 67% female) and 14 a diagnosis of SpA (mean age 62.2±8.8 years, 57% female) (Table I). For RA patients, 96% and 89% were positive for RF and ACPA, respectively. For SpA patients, 58% were positive for HLAB27 and 58% had psoriasis. The remaining 52 patients were considered to have PMR according to clinical ACR/EULAR criteria for PMR.

US results of patients fulfilling ACR/EULAR criteria for PMR

For the 52 patients initially considered to have PMR according to clinical ACR/EULAR criteria for PMR, shoulder US demonstrated US features of PMR in all (bilateral SAD bursitis, biceps tenosynovitis or GH effusion), thus fulfilling the US arm of PMR criteria.

We also searched for CPPD by US. CCPD diagnosis was confirmed by the presence of CPP crystals in synovial fluid of any joint analysis as recommended (11). Among the 52 patients

Table I. Baseline characteristics of patients with polymyalgia rheumatica (PMR), calcium pyrophosphate disease (CPPD), spondyloarthritis (SpA), rheumatoid arthritis (RA) and controls.

Baseline characteristics	PMR (n=27)	CPPD (n=25)	SpA (n=14)	RA (n=27)	Controls (n=23)
Age (years), mean ± SD	71.5 ± 8.5	79.8 ± 8.5	62.2 ± 8.8	61.3 ± 8.6	63.8 ± 11.6
Sex (% female)	52	88	57	67	61
DAS28, mean ± SD	NA	NA	NA	4.9 ± 0.8	NA
RF + (% of patients)	0	0	0	96	NA
ACPA+ (% of patients)	0	0	0	89	NA
BASDAI (0-100 mm), mean ± SD	NA	NA	52.7 ± 13.1	NA	NA
Psoriasis (% of patients)	NA	NA	58	NA	NA
HLAB27 + (% of patients)	NA	NA	58	NA	NA

SD: standard deviation; DAS28: Disease Activity Score in 28 joints; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; HLA: human leucocyte antigen; NA: not applicable.

Table II. Prevalence of ultrasonography (US) abnormalities in patients fulfilling the American College of Rheumatology/European League Against Rheumatism criteria for US-PMR criteria.

US features	PMR (n=27)	CPPD (n=25)	Controls (n=23)	p^*
SAD bursitis	26 (96.3)	17 (68.0)	1 (4.3)	p=0.0098
Long-head biceps tenosynovitis	23 (85.2)	18 (72.0)	2 (8.7)	p=0.317
Gleno-humeral effusion	13 (48.1)	17 (68.0)	0 (0)	p=0.171
Humeral bone erosion	2 (7.4)	11 (44.0)	4 (17.4)	p=0.003
AC synovitis	2 (7.4)	16 (64.0)	1 (4.3)	p<0.0001
AC chondrocalcinosis	1 (3.7)	23 (92.0)	5 (7.6)	p<0.0001

Data are n (%) or patients.
PMR: polymyalgia rheumatica; CPPD: calcium pyrophosphate disease; AC: acromioclavicular; SAD: subacromial and subdeltoid.
*comparing PMR and CPPD patients.

Table III. US performance for PMR and CPPD diagnosis.

US features	Sensitivity	Specificity	PPV	NPV
For PMR diagnosis				
SAD bursitis	96.3	35.8	37.7	96.0
Long-head biceps tenosynovitis	85.2	44.8	38.3	88.2
Gleno-humeral effusion	48.1	64.2	35.1	75.4
For CPPD diagnosis				
Humeral bone erosion	40.7	71.0	35.5	75.4
AC synovitis	59.3	85.5	61.5	84.3
AC chondrocalcinosis	85.2	97.1	92.0	94.4

PMR: polymyalgia rheumatica; CPPD: calcium pyrophosphate disease; AC: acromioclavicular; SAD: subacromial and subdeltoid; PPV: positive predictive value; NPV: negative predictive value

fulfilling ACR/EULAR criteria for PMR, 25 had a diagnosis of CPPD (Table I). Joint fluid analysis revealed PPC crystals in knees (n=13), shoulders (n=8), wrists (n=3) and ankle (n=1).

The remaining 27 without CPPD were classified as having PMR. CPPD patients were older (79.8±8.5 *vs*. 71.5±8.5 years, p=0.0009) and more frequently female (88% *vs*. 52%, p=0.007) than PMR patients. We observed no difference when disease duration was analysed (p=0.541).

The US abnormalities of PMR and CPPD patients are detailed in Table II. As compared with PMR patients, CPPD patients more frequently had humeral bone erosions (44% *vs*. 7.4%, p=0.003), AC synovitis (64% *vs*. 7.4%, p<0.0001) and AC chondrocalcinosis (92% *vs*. 3.7%, p<0.0001) but less frequently SAD bursitis (68% *vs*. 96.3%, p=0.0098). The two groups did not differ in frequency of biceps tenosynovitis (72% *vs*. 85.2%, p=0.317) or GH effusion (68% *vs*. 48.1%, p=0.17).

As compared with controls, PMR and CPPD patients more frequently had SAD bursitis (p<0.0001), long-head biceps tendon tenosynovitis (p<0.0001) and GH effusion (p<0.0001). As compared with controls, CPPD patients more frequently had humeral bone erosion (p<0.0001), AC chondrocalcinosis (p<0.0001) and AC synovitis (p<0.0001).

Performance of US for PMR and CPPD diagnosis as compared with other diagnoses

The diagnostic performance of the six US features for PMR and CPPD is detailed in Table III. After comparing patients with (n=27) and without (n=67) PMR, the most sensitive US features were SAD bursitis (96.3%) and long-head biceps tenosynovitis (85.2), but their specificity did not exceed 65%. For CPPD diagnosis, the US feature with the best ratio of sensitivity to specificity was AC chondrocalcinosis (sensitivity: 85.2%; specificity: 97.1%).

Discussion

Polymyalgic syndrome is characterised by inflammatory pain of shoulders and/or the pelvic girdle affecting older people (1). PMR is the most common condition associated with this syndrome, but many conditions can mimic PMR, notably RA, late-onset spondyloarthritis or CPPD. In this study, we aimed to define, by using US of shoulders, the prevalence of CPPD among patients with polymyalgic syndrome suspected to be PMR according to recent ACR/EULAR criteria. Almost half of the patients with polymyalgic syndrome had another diagnosis than PMR according to clinical and US arms of the ACR/EULAR criteria for PMR (8). Moreover, among patients with suspected PMR, almost half had CPPD. ACR/EULAR criteria for PMR (clinical and US arms) were validated in all patients with CPPD and polymyalgic syndrome. These results suggest that PMR criteria do not allow for excluding all frequent aetiologies of polymyalgic

syndrome, which limits the specificity of such criteria. This high rate of positive US patients could be explained by the fact that our patients were assessed in a tertiary university hospital. That could represent a bias of selection with more symptomatic or more selected patients than outpatients.

This relatively high frequency of CPPD among patients with suspected PMR was observed in a previous study published before the elaboration of ACR/EULAR criteria for PMR (15). In this study, 31% of patients with PMR also had CPPD. Another study found that 52% of patients with polymyalgic syndrome classified as PMR according to Bird criteria received another diagnosis when a large US screening was performed in association with usual biological tests (16). The other diagnoses were RA, SpA and CPPD. As suggested by these studies but also ACR/EULAR criteria for PMR, US can help the clinician distinguish PMR from mimicking conditions.

The PMR criteria recommend using US of shoulders and hips and analysing usual US features of PMR such as SAD or trochanteric bursitis, long-head biceps tenosynovitis, GH or hip effusion (8). Despite the high sensitivity of these US features, their specificity for PMR diagnosis seemed lower when the comparator was not healthy controls (17). In our study, SAD bursitis and long-head biceps tenosynovitis had high sensitivity but low specificity (<50%) when the comparators were other mimicking conditions (Table III). These data suggest that a search for usual US features of PMR had limited impact on the diagnosis but is useful to exclude the PMR diagnosis. This finding agrees with a previous study showing that usual US findings did not increase the sensitivity of ACR/EUAR criteria for PMR (7).

Falsetti *et al*. suggested performing US to assess hip, shoulders, wrists, knees, metacarpophalangeal joints and heels to better distinguish PMR from other conditions (16). However, this full-body US screening seems time-consuming in clinical practice. To increase the diagnostic accuracy of US without wasting time, we assessed the AC joint. Indeed, this joint can be easily assessed by US and is affected by CPPD. Moreover, AC joint and knee findings are well correlated for CPPD diagnosis (18). With US, we detected synovitis and CPPD of the AC joint in 64% and 92% of patients, respectively, with CPPD. The specificity of these two US features of CPPD was high in patients with polymyalgic syndrome (Table III). Also, humeral bone erosion was more frequent in CPPD than PMR patients but showed lower specificity. These results suggest that adding AC joint analysis to usual US assessment might provide better diagnostic accuracy.

We previously showed that US assessment of the AC joint might help differentiate SpA and RA in patients with painful shoulders, AC synovitis being more frequent in SpA than RA patients (14). In the present study, the specificity of AC synovitis (85%) was lower than AC chondrocalcinosis (Table III) because of the presence of SpA patients in the comparator group. Adding the detection of CPPD of the AC joint could help distinguish SpA from CPPD when AC synovitis is present.

Our study has some limitations. First, the number of patients was relatively low and US assessment was performed by one operator. However, the number of patients was similar to that in previous US studies and the US assessor was blinded to the diagnosis and clinical data. Additionally, we did not systematically assess hips, which could affect the specificity of usual US assessment. However, patients with other inflammatory rheumatic conditions such CPPD, RA or SpA can have US hip synovitis or trochanteric bursitis. In a study by Cantini *et al*., PMR patients with pelvic girdle symptoms were compared to controls with other rheumatic conditions. US hip synovitis and trochanteric bursitis were observed with similar frequency in both groups suggesting a low specificity of US features of PMR at hip level (19). Because hip involvement is less frequent than shoulder involvement (7), with lower diagnostic accuracy (20), we chose not to perform systematic US of hips. Finally, the detection of CPPD in patients with suspected PMR could be only an association in this older population. Interestingly, in a population of seronegative RA patients, CPPD was shown to mimic this condition, without apparition of bone erosion, suggesting that the prognosis could be different when CPPD was diagnosed (21). In addition, it was suggested that PMR patients with a six-month remission had more chance to maintain remission at one year than those without (22). As CPPD patients usually require shorter steroids therapy than other chronic rheumatic conditions, it could be relevant to analyse the presence of CPPD to determine patients with a short steroids therapy. However, in absence of longitudinal analysis, our study is unable to resolve this question and the therapeutic impact of CPPD diagnosis in PMR patients remains unclear.

In conclusion, detection of CPPD in patients with suspected PMR is relatively frequent. Adding US assessment of the AC joint to usual US screening might help the clinician better distinguish PMR from other conditions, notably CPPD.

Acknowledgement

We thank Laura Smales (BioMedEditing, Toronto, Canada) for copyediting.

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