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ORIGINAL ARTICLE

Clinical Features, Treatment and Monitoring in Patients With Polymyalgia Rheumatica

Fatma Gül YURDAKUL, Hatice BODUR, Filiz SİVAS, Bedriye BAŞKAN, Filiz ESER, Onur YILMAZ

Department of Physical Medicine and Rehabilitation, Ankara Numune Training and Research Hospital, Ankara, Turkey

ABSTRACT

Objectives: This study aims to evaluate the clinical symptoms and laboratory findings of Turkish patients with polymyalgia rheumatica.

Patients and methods: Clinical data of 41 patients (9 males, 32 females; mean age 65.5±7.6 years; range 60 to 80 years) with polymyalgia rheumatica were retrospectively evaluated. Patients' clinical symptoms, laboratory findings, therapies and therapeutic responses were analyzed.

Results: The most common symptoms were bilateral shoulder pain (59.9%) and morning stiffness (48.78%). Mean erythrocyte sedimentation rate at diagnosis was 66.8±22.5 mm/h, while mean C-reactive protein value was 48.7±25.8 mg/dL. In the third week of corticosteroid treatment, good response to treatment was detected in 33 patients (80.5%). Mean age of patients who gave good response to treatment (67.2±6.7) was higher than mean age of patients who gave poor or no response to treatment (58.5±7.8) (p=0.009).

Conclusion: Patients' clinical features, laboratory findings, initial steroid doses, and responses to corticosteroid therapy were consistent with the literature. However, the rate of morning stiffness was high and peripheral arthritis was rare. Giant cell arteritis was not detected in patients with polymyalgia rheumatica. Good response to early steroid treatment was observed in older patients. Rate of relapse was low. Further studies are required to evaluate factors affecting response to treatment, remission, and relapse.

Keywords: Clinical features; polymyalgia rheumatica; treatment response.

Polymyalgia rheumatica (PMR) is a chronic, inflammatory disorder characterized by morning stiffness, aching in the shoulder, and pelvic girdles in people aged 50 years and older.[1] In 1888, Bruce described PMR as senile rheumatic gout with proximal muscular syndrome.[2] To the best of our knowledge, there are no specific diagnostic tests for PMR. Diagnosis is based on clinical presentation, evidence of systemic inflammation, and response to corticosteroids. Over the years, various classification criteria have been developed by Bird et al.,[3] Chuang et al.,[4] and Healey.[5] More recently, new classification criteria have been developed by a group of international specialists with the official endorsement of the American Collage of Rheumatology and of the European League Against Rheumatism.[6] A new scoring algorithm was developed based on morning stiffness (>45 minutes), hip pain and/or limited range of motion, ultrasound findings absence of rheumatoid factors (RF) and/or anti-citrullinated protein antibodies, and absence of peripheral joint pain. Adding ultrasound into the criteria increased the specificity and was helpful for differential diagnosis testing. Conversely, response to corticosteroids was not included in new classification criteria due to the possibility of several conditions giving false positive responses to treatment.[6] There are several studies about the epidemiology, clinical characteristics, and treatment options of patients with PMR.[7-15] To our knowledge, the epidemiological study of PMR within Turkish patients is limited in the literature. In this study, we aimed to evaluate the clinical symptoms and laboratory findings of Turkish patients with PMR. Additionally,

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Correspondence: Fatma Gül Yurdakul, M.D. Ankara Numune Eğitim ve Araştırma Hastanesi Fizik Tedavi ve Rehabilitasyon Kliniği, 06100 Altındağ, Ankara, Turkey.
Tel: +90 505 - 925 42 14 e-mail: fatmagulonder@gmail.com

therapeutic responses as well as relapses and remissions were evaluated.

PATIENTS AND METHODS

A total of 41 patients (9 males, 32 females; mean age 65.5±7.6 years; range 60 to 80 years) who were being followed-up at least for one year in the Department of Physical Medicine and Rehabilitation were included. Information about patients' clinical characteristics, demographic data, concomitant diseases, family history, and treatment regime were obtained retrospectively from the records. Patients were classified as PMR according to Bird's criteria: *(i)* bilateral shoulder pain and stiffness or both; *(ii)* onset of illness within two weeks; *(iii)* initial erythrocyte sedimentation rate (ESR) >40 mm/h; *(iv)* duration of stiffness >1 h; *(v)* age 65 years or older; *(vi)* depression or weight loss or both; and *(vii)* bilateral upper arm tenderness. If three or more of the seven criteria were fulfilled, a diagnosis of probable PMR was made.[3] Additionally, initial symptoms and signs, physical examination findings, and complaints which were added during the follow-up were analyzed. Laboratory findings including compound blood account, ESR, C-reactive protein (CRP), RF, and liver and kidney function tests were collected.

Treatment for osteoporosis and gastric symptoms were observed. Patients receiving bisphosphonates and/or calcium and vitamin D preparations for osteoporosis were evaluated. The use of proton pump inhibitors or H_2 antagonists for gastric symptoms was assessed.

Initial dose of corticosteroids, use of disease-modifying antirheumatic drugs (DMARDs) therapy, response to corticosteroids, and remission and relapse were detected. Steroid doses were calculated as daily prednisolone equivalents. Response to treatment was evaluated in two parts: *(i)* good response and *(ii)* poor/no response. Good response was defined as completely or almost completely improved clinical symptoms with significantly reduced acute phase reactants, and normal levels of ESR and/or CRP within three weeks of starting steroid treatment. Poor response was defined as insufficiently improved clinical symptoms and levels of acute phase reactants in the first three weeks of treatment. No response was defined as insignificant or no changes in symptoms and acute phase reactants in the first three weeks. Remission was defined as the absence of clinical symptoms and normal levels of acute phase reactants without using any drugs which controls PMR. Relapses were defined as reappearance of clinical symptoms with elevated ESR or CRP levels in a patient receiving steroid treatment or after disuse of steroids.

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 18.0 (SPSS Inc., Chicago, IL, USA) software program. Simple descriptive statistics including mean, median, and standard deviation were used to describe the data. Comparisons were performed using Mann-Whitney U test for continuous variables and either Chi-square test or Fisher's exact test for categorical variables. Statistical significance was defined as a p value ≤0.05.

RESULTS

An investigation of presence of any comorbid chronic diseases revealed that seven patients had diabetes mellitus, four had coronary artery disease, one had hypothyroidism, one had chronic renal failure, and 20 had hypertension. Table 1 shows the baseline demographics of the study population.

Most common symptoms were bilateral shoulder pain (59.9%) and morning stiffness (48.78%). Peripheral arthritis was detected in four patients, two having knee arthritis, one having

Table 1. Baseline demographics of patients with polymyalgia rheumatica

	n	%	Mean±SD
Age at onset of symptoms (years)			65.5 ±7.6
<50	2	4.87	
>80	2	4.87	
60-80	33	80.48	
Sex			
Female	32	78.04	
Male	9	21.96	
Existing chronic disease			
Hypertension	20	48.78	
Diabetes mellitus	7	17.07	
Coronary artery disease	4	9.75	
Chronic renal failure	1	2.43	
Hypothyroidism	1	2.43	

SD: Standard deviation.

Table 2. Clinical characteristics of patients with polymyalgia rheumatica

Primary symptoms	n	%	Mean±SD
Bilateral shoulder pain	23	59.09	
Morning stiffness	20	48.78	
Myalgia	16	39.02	
Hip girdle	8	19.50	
Fatigue	7	17.07	
Distal arthritis	4	9.75	
Erythrocyte sedimentation rate (mm/h)			66.8±22.5
<20 mm/h (normal)	2	4.87	
C-reactive protein (mg/dL)			48.7±25.8
≤1 mg/dL (normal)	3	7.31	

SD: Standard deviation.

wrist arthritis, and one having wrist arthritis with metacarpophalangeal joints. None of the patients was diagnosed as giant cell arteritis. Mean ESR at diagnosis was 66.8±22.5 mm/h with two of the patients (4.87%) having normal ESR (<20 mm/h). Mean CRP was 48.7±25.8 mg/dL and normal CRP (≤1 mg/dL) was observed in three patients. RF values of 36 patients were obtained and a positive RF was determined in 8.33% (n=3) of patients. Table 2 shows clinical characteristics and laboratory findings of the patients.

Dyspeptic complaints of patients and the use of drugs for gastric symptoms were evaluated. Gastric prophylaxis (with proton pump inhibitors or H_2 antagonists) was prescribed to 34 patients (82.9%). Thirteen patients (31.7%) had a history of dyspeptic symptoms before the diagnosis of PMR.

Twenty-six patients (63.41%) received a prescription for osteoporosis (bisphosphonate and/or calcium + vitamin D). Nine patients (21.95%) were using calcium + vitamin D supplements alone while 17 patients (41.5%) were using bisphosphonate and calcium + vitamin D supplements together. The remaining 15 patients did not use any drug for osteoporosis.

Mean initial dose of steroid was 17.4±4.2 mg/day. The most frequent starting dose was 20 mg/day (in 56.1% of patients), while the second was 15 mg/day (in 26.8% of patients). Six patients (14.6%) had received 10 mg/day, and one patient (2.4%) had received 30 mg/day prednisolone at the beginning of the treatment. Good response to initial steroid was observed in 33 patients (80.5%) in the first three weeks of treatment. Eight patients had poor or no response in the first three weeks. Patients with an inadequate response to steroid treatment had received a higher dose of prednisolone according to their clinical and laboratory findings. Improved clinical symptoms and normal ESR/CRP were observed in six patients after increasing steroid dose. DMARD (methotrexate; MTX) was used in two patients (4.87%). MTX was started with a dose of 10 mg/week.

We evaluated age, sex, distal arthritis, ESR, CRP, and dose of initial steroid in patients with or without good response in the first three weeks. Mean age of patients who had good response was 67.2±6.7, whereas mean age of those with poor/no response was 58.5±7.8 (p=0.009). Table 3 shows the analysis of clinical characteristics and laboratory findings in the good response and poor/no response groups.

Seven patients (17.1%) had remission and six patients (14.63%) had relapse at least once during the monitoring. Two patients had more than two relapses. Two patients had relapse after the remission and four patients had relapse when they were still receiving steroid treatment.

Table 3. Clinical characteristics and laboratory findings in groups of good response and poor/no response

	Good response group (n=33)			Poor/no response group (n=8)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age			67.2±6.7			58.5±7.8	0.009
Female	27	81.8		5	62.5		0.342
Peripheral arthritis	2	6.1		2	25.0		0.165
Erythrocyte sedimentation rate (mm/h)			66.2±26.4			62.3±7.5	0.974
C-reactive protein (mg/dL)			48.3±28.1			45.1±29.3	0.754
Initial prednisolone dose (mg/day)			18.0±3.9			15.0±4.6	0.088
Remission	6	18.01		1	12.5		0.702

SD: Standard deviation.

DISCUSSION

Polymyalgia rheumatica is a common chronic inflammatory disease that develops in older persons who are conventionally treated with long-term corticosteroids.[6] We described clinical features of patients with PMR and analyzed their therapeutic responses. PMR typically affects people 50 years of age or older and its incidence increases with age, peaking at 70-80 years.[7,8] In our patient population, only two patients (4.87%) were under the age of 50 and 80.48% of the patients were between the ages of 60 and 80. It is known that females are affected two or three times more frequently than males.[9] One retrospective cohort study which included 304 patients reported that 75.3% of the patients were female.[10] Higher female patient ratio with PMR changes between 55.26% and 69.64% was showed in a review, which was published in 2009.[11] Likewise, significant female domination (78.08%) was demonstrated in our study.

Hallmark symptoms of PMR include aching and prolonged morning stiffness in the shoulder girdle. Nearly all patients develop shoulder pain, while neck and pelvic girdle pain can also be present (approximately 70% and 50% of patients).[12] Helliwell *et al.*[10] reported that the most common symptom (45.7%) was bilateral shoulder pain. Lee *et al.*[13] reported that both shoulder and hip girdle pain were the most common symptoms (60.3%) and shoulder girdle pain was seen in 25.7% of the patients. In our study population, the most common symptom was bilateral shoulder pain (59.09%) followed by morning stiffness (48.48%).

About 40% of PMR patients were reported to have systemic symptoms including low-grade fever, depression, fatigue, and weight loss.[14] In our study, seven patients (17.7%) developed fatigue and 16 patients (39.2%) complained of severe myalgia.

Nearly half of the patients with PMR have distal musculoskeletal manifestations. In particular, one quarter of patients had arthritis, mainly of knees (40%) and wrists (40%). Metacarpophalangeal joints involvement was less common and could mimic rheumatoid arthritis. In a minority (about 12%) of patients, distal tenosynovitis and distal extremity swelling which is often referred to as RS3PE (remitting seronegative symmetrical synovitis with pitting edema) syndrome, was observed. Carpal tunnel syndrome in PMR has also been noted.[15] Ceccato *et al.*[16] showed that 39% of patients who had peripheral synovitis presented with pitting edema (5%), carpal tunnel syndrome (5%), and distal tenosynovitis (1.3%). In our 41 patients with PMR, four patients (9.8%) developed distal arthritis and 50% of distal arthritis was knee arthritis. Carpal tunnel syndrome was not detected in these patients while monitoring for PMR. In this study, majority of the clinical features at presentation were similar to several previous reports from the literature although higher rates of morning stiffness and rare peripheral arthritis were observed in our patients.

Polymyalgia rheumatica is typically associated with giant cell arteritis (GCA). Population based studies have shown that 16-21% of patients with PMR have GCA, while PMR can also be present (40-60%) in patients with GCA.[12] In an epidemiological study from Korea, there was no GCA in patients with PMR.[13] Similar to Korean patients, no GCA was detected in our study. This result may be associated with the ethnic differences.

Serious adverse events were reported due to the chronic use of low dose corticosteroids. In particular, increased osteoporotic fractures and cardiovascular disease draw attention.[17] The use of bone protection when initiating steroids for PMR to prevent the complications of osteoporosis is recommended in the British Society for Rheumatology and British Health Professionals in Rheumatology guidelines for the management of PMR.[18] Helliwell *et al.*[10] reported that 4% of the patients in their study developed osteoporosis and 60.0% of the patients received prophylaxis for osteoporosis. In our study, 26 patients (63.41%) received a prescription for osteoporosis (bisphosphonate and/or calcium + vitamin D). Nine patients (21.95%) were using calcium + vitamin D supplements alone while 17 patients (41.5%) were using bisphosphonate and calcium + vitamin D supplements together. Helliwell *et al.*[10] reported that 18.4% of the patients complained of dyspeptic symptoms and 28% of the patients received prophylaxis for gastric symptoms. In our study, proton pump inhibitors or H_2 antagonists were prescribed to 82.9% of the patients.

Our approach to osteoporosis prophylaxis was similar to the literature, although gastric prophylaxis was more common in our patients. Recommendations for osteoporosis prophylaxis are mentioned frequently in the guidelines for PMR; however, no detailed information is available about gastric prophylaxis. Approaches to gastric prophylaxis may be different according to expert opinion, and patient population.

The standard treatment for PMR is low-dose glucocorticoids, which characteristically induce the rapid resolution of symptoms.[19] The British Society for Rheumatology and British Health Professionals in Rheumatology guidelines suggested 15 mg/day prednisolone for the first three weeks for the management of PMR. The suggested regimen is *(i)* daily prednisolone 12.5 mg for the second three weeks, *(ii)* 10 mg for 4-6 weeks, and *(iii)* then reduction by 1 mg every 4-8 weeks.[18] However, initial prednisolone doses were reported differently in the literature as 21.5±8.3 mg/day, 15±4 mg/day, 15.8±8.4 mg/day.[10,13,17] The most common starting doses were ≥15 mg/day in these studies. In our study, mean prednisolone dose was 17.4±4.2 mg/day. The majority of the patients (56.1%) received 20 mg/day prednisolone.

Helliwell *et al.*[10] reported that 72.7% of their patients had good response to corticosteroids and Lee *et al.*[13] reported that approximately 40% of their patients had normal ESR in the first four weeks. Similarly, good response to the initial steroid was seen in 80.5% of patients in our study. It is known that PMR usually responds well to corticosteroids but not always. It seems that older patients may have better response to early treatment. Still, further studies are needed to determine the effect of age on the PMR treatment.

Disease-modifying antirheumatic drug therapy is recommended by British Society for Rheumatology and British Health Professionals in Rheumatology after two relapses.[18] In a randomized double blind placebo controlled study, two groups were compared one of which received prednisolone and MTX 7.5 mg/week, while the other was treated by prednisolone and placebo. At the end of the second year, no differences were detected between the MTX group and the placebo group concerning time to achieve remission, duration of remission, number of relapses, or cumulative prednisolone doses.[20] Similarly, in two studies published in 2004 and 2007, no differences were found between the MTX group and placebo group cumulative prednisolone doses.[21,22] In several clinics, DMARDs (azathioprine, leflunomid and hydroxychloroquine) have been used for separating patients from corticosteroids.[13,23,24] Corticosteroid-related adverse events have occurred frequently, particularly in patients with relapsing disease. Consequently, new studies about the treatment of PMR with tocilizumab have drawn attention.[25,26] Lee *et al.*[13] reported that 30.8% of the patients used MTX and 61.5% of the patients used hydroxychloroquine. In our clinic, MTX is not used as a routine practice in patients with PMR. Two patients (4.87%) received MTX, while the rest of the patients received prednisolone for the treatment of PMR. According to these results, our treatment approach seems more conservative and traditional.

Remission and relapse were evaluated in the patients. Seven patients (17.1%) had remission and six patients (14.6%) had relapse at least one time in our study. Lee *et al.*[13] reported that 20.5% of their patients had remission and 46.1% of their patients had relapse. In another study from Korea, remission was reported for 15.7% and relapses were reported for 68.3% of the patients.[27] Our relapse rate was lower than these reports; however, further studies with larger patient populations are needed to clarify the factors affecting relapse.

In conclusion, in our study, majority of the clinical features, initial steroid doses, and responses to corticosteroid therapy were similar to previous reports in the literature. Our patients with PMR were not associated with GCA. Good response to early steroid treatment was observed in older patients. Relapse rates were fairly low. Nevertheless, further studies are needed to evaluate the factors that affect response to treatment, remission, and relapse.

Declaration of conflicting interests

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