Autoimmunity Reviews xxx (xxxx) xxx

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Impact of age at diagnosis in polymyalgia rheumatica: A retrospective cohort study of 218 patients

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ARTICLE INFO

Keywords:
Polymyalgia rheumatica
Age
Relapse
Glucocorticoids

ABSTRACT

Background: Polymyalgia rheumatica (PMR) is a common musculoskeletal inflammatory disease that may occur with giant-cell arteritis (GCA) or in an isolated form. While the incidence is highest in the elderly, there is a paucity of data on its presentation, clinical course and response to treatment in younger individuals.
Methods: We conducted a retrospective review of 40 patients who were diagnosed with isolated PMR under the age of 60 and 178 patients diagnosed above this age, taking into account clinical and laboratory data and treatment history.
Results: Patients who were diagnosed at a younger age had lower acute-phase reactant levels at diagnosis but not after initiation of treatment or at the time of relapse. The risk of relapse was lower in the group diagnosed under age 60 (35% vs 55%). Cumulative and maximal glucocorticoid doses, use of glucocorticoid-sparing agents and duration of glucocorticoid treatment, did not differ between the groups. In multivariate analysis, younger age at diagnosis was associated with cervical pain and male gender.
Conclusion: Compared to patients diagnosed above age 60, patients diagnosed with PMR at a younger age have a lower risk of relapse, but similar long-term outcomes with regards to continued need for treatment.

1. Introduction

Polymyalgia rheumatica (PMR) is a common inflammatory disorder that usually presents in patients over 50 years of age, characterised by girdle pain in the shoulders and hips, cervical or lumbar spine pain, morning stiffness, and increased inflammatory parameters that often respond promptly to treatment with glucocorticoids [1]. The clinical course is variable however, and around half of patients suffer relapses, requiring re-intensified treatment which exposes patients to the significant risks of long-term glucocorticoid use [2–4]. PMR may be found as an isolated phenomenon or in association with giant cell arteritis (GCA) [5].

In other rheumatic diseases, including ANCA-associated vasculitis and rheumatoid arthritis, age may have a significant impact on the clinical phenotype, prognosis, or response to treatment [6–8]. Delaval et al. recently conducted a retrospective study in GCA patients aged between 50 and 60 years at onset and compared them to GCA patients aged over 60 years [9], finding differences in presentation (predominantly large-vessel involvement versus cranial disease) and more refractory disease in younger patients.

In 2018, Charpentier et al. analyzed a cohort of 42 patients with PMR, comparing 14 patients aged between 50 and 60 years at onset to patients aged over 60 years [10]. They found that young patients with PMR were mostly men and were more dependent on corticosteroids compared to elderly patients. Prior research on factors determining timing of relapses, had not identified age as a significant factor [3]. To further elucidate the role of age in the clinical presentation, laboratory findings, disease course, and treatment response of polymyalgia rheumatica, we conducted a retrospective analysis of 218 patients with isolated PMR.

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https://doi.org/10.1016/j.autrev.2020.102692
Received 8 May 2020; Accepted 15 May 2020
Available online 22 October 2020

2. Methods

2.1. Patients

We collected data from a local registry of patients diagnosed with polymyalgia rheumatica from January 2000 through December 2017 in the outpatient clinic or hospitalisation unit of the General Internal Medicine department of the University Hospitals of Leuven, Leuven, Belgium. Patients were eligible for inclusion if they were newly diagnosed with isolated PMR during this time period. The diagnosis of isolated PMR was based on the judgment of an experienced clinician (DB and SV) after a 6-month follow-up period, taking into account all available information (clinical data and evolution, biochemical, radiological, and PET results).

In our centre, the standard treatment for PMR consists of 15 mg prednisone equivalent/day as starting dose for 4 weeks, followed by 10 mg/day for 6 weeks, 7.5 mg/day for 6 weeks, 5 mg/day for 8 weeks, 2.5 mg/day for another 8 weeks, after which treatment is discontinued if no relapses occur. Hence, the total treatment duration typically lasts 32 weeks in uncomplicated cases. The standard follow-up is organised 2 weeks after the initial diagnosis, 4 weeks after the first dose reduction, and every 3 months thereafter for 32 weeks with extra visits for relapses or adverse events. After 32 weeks, the follow up interval may vary between 3 and 6 months. However, both treatment duration and follow-up may be adjusted on an individual basis.

We excluded patients with evidence of giant-cell arteritis at the time of the initial presentation; patients who developed GCA after initial remission of PMR were not excluded. Patients were also excluded if a likely alternative diagnosis explained their symptoms, either at presentation or later in the course of their illness, or in case of features of systemic illness that were not well explained by PMR. Patients were also excluded if they were receiving glucocorticoid treatment for another diagnosis. Patients with distal symptoms, including remitting seronegative symmetric synovitis and pitting edema (RS3PE-syndrome), were not excluded as this is deemed to be a variant presentation of the same spectrum as polymyalgia rheumatica [11–14].

This study was approved by the Ethical Research Committee of the University Hospitals of Leuven, Belgium. Informed consent was waived because of the retrospective nature of the study and the analysis used anonymised clinical data.

2.2. Data collection

For each patient, we collected the following clinical data from the Electronic Health Record if available: manifestations at disease onset including fever, anorexia/weight loss, shoulder girdle pain, hip girdle pain, cervical and lumbar spine pain; presence and duration of morning stiffness; comorbidity (GCA and RS3PE); time until disease control; presence and timing of relapse(s).

Relapse was defined as need for a restart or an increase of the dose of glucocorticoids, or addition of a glucocorticoid-sparing agent, in patients who had earlier had clinical improvement on treatment.

We determined maximal doses of glucocorticoids as well as cumulative doses at one and three months (expressed as milligrams of prednisone equivalent). Use of glucocorticoid-sparing agents was also noted. Laboratory data included presence of rheumatoid factor or anti-citrullinated cyclic polypeptide antibodies, as well as erythrocyte sedimentation rate and blood levels of haemoglobin, and CRP at diagnosis, at follow-up visit and at the time of first relapse, if any.

2.3. Analysis

Data are presented as the mean ± standard deviation (SD) or as the median and interquartile range, as appropriate, for continuous variables and frequency (percentage) for categorical variables. Quantitative variables were compared using Student's *t*-test or nonparametric tests (Mann-Whitney *U* test, or Wilcoxon signed rank test, as appropriate) and categorical variables were compared using Fisher's exact test or the chi-square test. Multivariable analysis was performed using a logistic regression. We included characteristics that differed between the groups with $p < 0.30$. All analyses were performed using the SPSS software (version 26, IBM corp.). All statistical tests were two-sided, and significance was set at the 0.05 level.

3. Results

From 304 patient records screened, we identified 270 patients with PMR and excluded 29 patients with a likely alternative diagnosis (Fig. 1). After exclusions, a total of 218 patients with isolated PMR were included in the final analysis. Ninety-seven patients had complete data to allow classification by the ACR/EULAR criteria. Of these 97 patients, 62 (66%) met classification criteria.

In the final cohort, 40 patients were diagnosed at an age of 60 years old or younger (the $PMR_{\leq 60}$ group), and 178 were diagnosed above this age (the $PMR_{>60}$ group). In the $PMR_{\leq 60}$ group, 53% of patients with complete data met the ACR/EULAR classification criteria, as compared to 70% of patients in the $PMR_{>60}$ group ($p = 0.66$).

3.1. Clinical, laboratory and imaging characteristics

Table 1 shows the presenting characteristics of our patient cohort, stratified by age at diagnosis. The median age at diagnosis was 55 (IQR 49–57) for the $PMR_{\leq 60}$ group, and 72 (IQR 67–77) for the $PMR_{>60}$ group. The youngest age at diagnosis in the cohort was 44 years old, while the eldest was 88. 40% of the $PMR_{\leq 60}$ patients were female, compared to 57% of the $PMR_{>60}$ group, a trend that fell short of significance ($p = 0.05$).

In the $PMR_{\leq 60}$ group, 55% presented with isolated musculoskeletal complaints, in the absence of any systemic symptoms, while anorexia or weight loss were noted in 27% and fever in 17%. Most patients had shoulder (90%) and hip (80%) pain, while pain at the cervical and lumbar spinal level were documented for 32% and 20%, respectively. Morning stiffness was noted in 70%. None of these characteristics were significantly different from the $PMR_{>60}$ group.

Compared to the $PMR_{>60}$ group, those in the $PMR_{\leq 60}$ group had significantly lower absolute values of CRP (median of 36.5 v 49.6 mg/L; $p = 0.02$) and ESR (median of 42.5 v 56.0 mm/h; $p = 0.005$), and higher haemoglobin levels (median of 13.0 v 12.0 g/dL; $p = 0.01$) at diagnosis. After initiation of treatment, and at the time of first relapse, these differences were no longer detectable. A statistically significant difference in ESR remained after initiating treatment. 15% of patients in the $PMR_{\leq 60}$ group, and 14% of those in the $PMR_{>60}$ group, had only low-grade biochemical signs of inflammation (CRP $\leq$ 10 mg/L) at diagnosis ($p = 1$).

We conducted multivariate analysis to identify any clinical characteristics that are independently associated with younger age at presentation. As shown in Table 2, patients in the $PMR_{\leq 60}$ group were less likely to be female (OR 0.47; $p = 0.03$) and more likely to report pain in the cervical region (OR 2.49; $p = 0.04$). No other characteristics reached statistical significance.

3.2. Treatment and clinical course

All of the patients in the $PMR_{\leq 60}$ group and 175/178 patients in the $PMR_{>60}$ group received first-line treatment with glucocorticoids; in the $PMR_{>60}$ group, 2 patients with mild symptoms were managed symptomatically and 1 patient had an initial spontaneous remission, but did receive glucocorticoids later for a relapse.

Treatment regimens and outcomes are summarised in Table 3. In patients with sufficient data to calculate cumulative doses, the cumulative prednisone equivalent dose at 28 days was 460 mg (IQR 420–560 mg) in the $PMR_{\leq 60}$ group and 420 mg (IQR 415–525 mg) in the $PMR_{>60}$

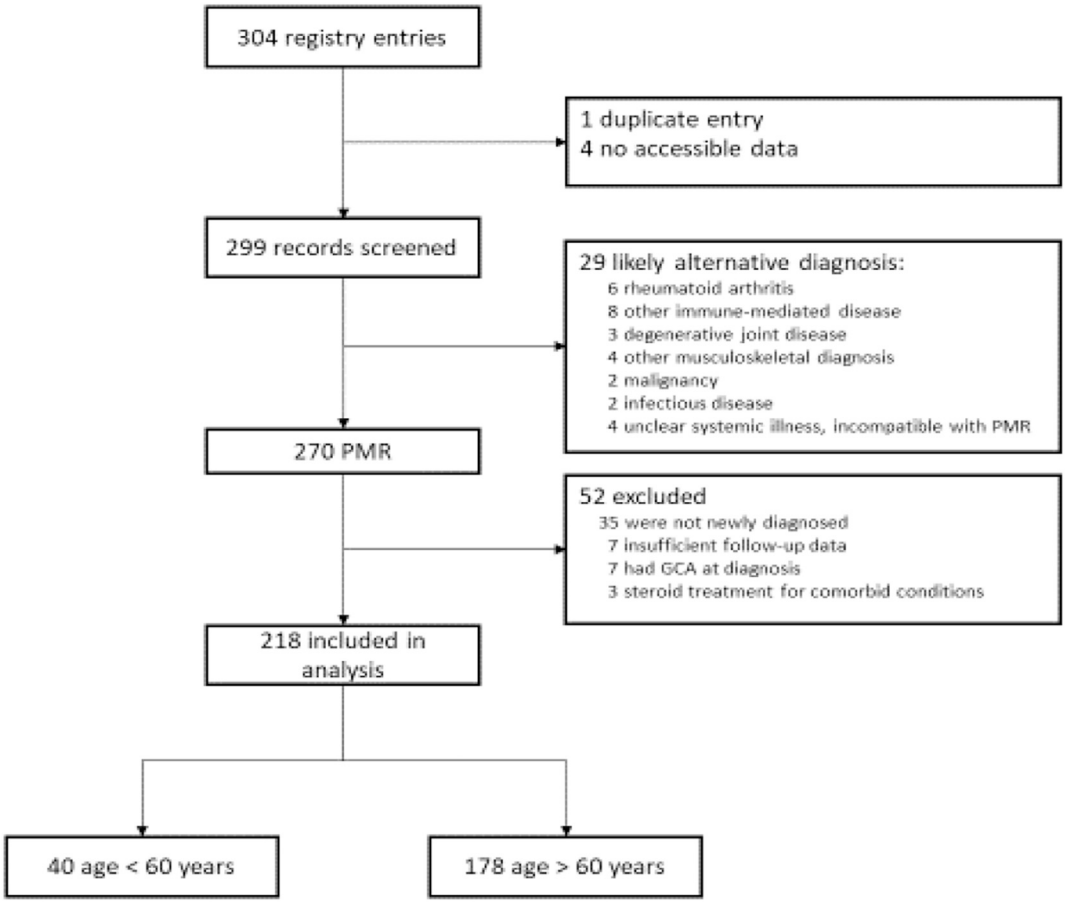

Fig. 1. Inclusion process.

Table 1
Clinical and laboratory characteristics.

Characteristics	$PMR_{\leq 60}$ (n = 40)	$PMR_{>60}$ (n = 178)	*P*-value
Demographics			
Female	16 (40%)	101 (57%)	0.05
Age at diagnosis	55 (49–57)	72 (67–77)	–
Clinical manifestations			
Isolated musculoskeletal symptoms	22 (55%)	106 (60%)	0.79
Fever	7 (17%)	20 (11%)	0.29
Anorexia or weight loss	11 (27%)	62 (35%)	0.46
Morning stiffness	28 (70%)	109 (61%)	0.29
Shoulder girdle pain	36 (90%)	166 (93%)	0.50
Cervical spine pain	13 (32%)	33 (18%)	0.05
Lumbar spine pain	8 (20%)	35 (20%)	1
Hip girdle pain	32 (80%)	145 (81%)	0.82
Laboratory values at diagnosis			
CRP (mg/L)	36.5 (21.0–61.6)	49.6 (19.9–48.5)	0.02
ESR (mm/h)	42.5 (29.5–57.5)	56 (40.0–81.0)	0.005
Haemoglobin (g/dL)	13 (12.6–14.0)	12 (10.9–13)	0.01
Patients with CRP $\leq$ 10 mg/L	6 (15%)	25 (14%)	1

PMR, polymyalgia rheumatica; n, number; IQR, interquartile range; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate. Continuous variables are given as the median, with the first and third quartiles given in brackets.

group. At 86 months cumulative doses had risen to 1152.5 mg (IQR 980–1265 mg) for the $PMR_{\leq 60}$ group and 1050 mg (IQR 953.75–1187.5 mg) for the $PMR_{>60}$ group. Differences between the groups were not statistically significant.

Table 2
Factors associated with PMR ≤60 in multivariate analysis.

	OR	CI 95%	*P*-value
Female gender	0.47	0.23–0.96	0.04
Fever	2.25	0.83–6.13	0.11
Morning stiffness	1.30	0.60–2.82	0.50
Cervical spine pain	2.49	1.12–5.54	0.03

OR, Odds ratio; CI, Confidence intervals.

Compared to $PMR_{>60}$ patients, those in the $PMR_{\leq 60}$ group were less likely to relapse after their initial treatment (35 vs 55%; $p = 0.02$). 57% of $PMR_{\leq 60}$ patients who relapsed, did so within a year after starting treatment, a similar proportion to the $PMR_{>60}$ group (53%; $p = 1$). There was a nonsignificant trend toward less frequent diagnosis of GCA at the time of a relapse for the $PMR_{\leq 60}$ group (10% of $PMR_{\leq 60}$ patients, versus 24% of $PMR_{>60}$ patients, $p = 0.06$).

Of the $PMR_{\leq 60}$ patients, 15% were treated with glucocorticoids for less than a year, 64% for 1–4 years and 21% had not been able to discontinue glucocorticoids after more than 4 years of treatment, a similar distribution to the $PMR_{>60}$ group. Glucocorticoid-sparing agents were used in 15% of the $PMR_{\leq 60}$ group and 14% of the $PMR_{>60}$ group ($p = 0.81$). Methotrexate and azathioprine were the predominantly used agents in both groups. None of the patients in the $PMR_{\leq 60}$ group required more than 1 glucocorticoid-sparing agent to be used, as compared with 3% of those in the $PMR_{>60}$ group; this difference was not statistically significant ($p = 0.59$). One patient in the $PMR_{>60}$ group received tocilizumab as a third glucocorticoid-sparing agent.

PMR, polymyalgia rheumatica; GCA, giant-cell arteritis; RS3PE, remitting seronegative symmetrical synovitis with pitting edema.

Table 3
Management and clinical course.

Characteristics	$PMR_{\leq 60}$ (n = 40)	$PMR_{>60}$ (n = 178)	P-value
Glucocorticoid treatment			
Cumulative dose 28 days	460 (420–560) n = 38	420 (415–525) n = 171	0.19
Cumulative dose 86 days	1153 (980–1265) n = 37	1050 (954–1188) n = 165	0.29
Maximal dose	20 (15–20)	20 (15–20)	0.5
Treatment duration			
≤ 12 months	5 (15)	17 (12)	0.62
12–47 months	21 (64)	93 (65)	0.84
≥48 months	7 (21)	32 (23)	1
Effect on acute phase reactants			
CRP, after initiating therapy (mg/L)	1.4 (1.0–6.4)	3.9 (1.3–8.7)	0.26
CRP, at first relapse (mg/L)	9.2 (2.0–31.7)	15.4 (8.0–26.0)	0.36
ESR, after initiating therapy (mm/h)	10 (7.0–16.0)	16 (8.0–30.0)	0.04
ESR, at first relapse (mm/h)	13.5 (7.8–27.3)	27 (14.3–40.0)	0.13
Relapse			
Total	14 (35)	98 (55)	0.02
Early (≤1 year)	8 (57)	52 (53)	1
Comorbidity			
GCA diagnosis at relapse	4 (10)	51 (24)	0.06
RS3PE	2 (5)	16 (9)	0.75
Glucocorticoid-sparing agents			
2nd-line	6 (15)	25 (14)	0.81
methotrexate	5	13	
azathioprine	1	10	
hydroxychloroquine	0	1	
cyclophosphamide	0	1	
3rd-line	0 (0)	5 (3)	0.59
azathioprine	0	3	
methotrexate	0	2	
4th-line	0 (0)	1 (0.6)	1
tocilizumab	0	1	

Glucocorticoid doses are expressed as mg of prednisone equivalent.

4. Discussion

To our knowledge, our study is the largest retrospective analysis to date to determine the impact of age on the clinical presentation, laboratory findings, disease course, and treatment response in patients with isolated polymyalgia rheumatica.

The retrospective analysis of 42 patients with PMR by Charpentier et al. described individuals with PMR of 60 years or younger as a different subset of patients. Sixty-five percent of these patients were men in contrast to recent epidemiological studies reporting 64% of PMR cases occurring in women [10,15]. We can confirm that more patients tended to be male in our $PMR_{\leq 60}$ group. Patients in the $PMR_{\leq 60}$ group also tended to present more often with inflammatory pain in the cervical region compared to the $PMR_{>60}$ group. Both findings were statistically significant in multivariate analysis but not in univariate analysis. Future research is needed to confirm whether true differences in presentation, based on age, exist.

The young PMR patients in the retrospective analysis by Charpentier et al. were also significantly more often dependent on corticosteroids [10]. However, our study results do not provide evidence for a more severe presentation in patients diagnosed at a younger age. Patients with isolated PMR in the $PMR_{\leq 60}$ group and the PMR > 60 group received similar courses of glucocorticoids for a similar total duration, irrespective of age. In addition, the highest dose of corticosteroids required to achieve disease control throughout the entire treatment duration as well as the need for glucocorticoid-sparing agents did not differ significantly between the groups.

We found the risk of disease relapse to be slightly higher in the $PMR_{>}60$ group. Serum acute-phase reactants at diagnosis were also higher in this group. The clinical relevance of this finding is unclear, as the total duration of treatment was not impacted by the difference in relapse risk, and differences in CRP remitted after initiation of treatment. Prior research has shown persistently raised CRP after initiation of treatment to be a more powerful prognostic marker than raised acute phase reactants at diagnosis [4].

Our study has several strengths. Primarily, we examined a relatively large sample of patients with isolated PMR (218 in total). The exclusion of patients with associated GCA at diagnosis precludes age-dependent presentations of GCA [9] confounding the data. In addition, multiple outcomes pertaining to disease severity (relapse likelihood and timing, maximal and cumulative doses of glucocorticoids, need for glucocorticoid-sparing agents, and total duration of glucocorticoid treatment) were recorded, to allow for the possibility that more aggressive treatment of younger patients masked a more severe presentation of the disease.

There are also several limitations to our study. First, retrospective studies are of course inherently subject to variation in the completeness of data. This design also precludes adjusting for unanticipated confounding factors. Second, the limited sample size of the $PMR_{\leq 60}$ group implies a lack of power to find more subtle differences between the groups. As our study spans two decades, there may also be some heterogeneity within the groups, as understanding of the disease and its treatments evolved over time. Finally, the findings from our single-centre study may be difficult to generalise to a broader population.

A significant percentage of included patients in our retrospective cohort were not classifiable by EULAR/ACR criteria for PMR. Twenty-five percent of $PMR_{\leq 60}$ patients were systematically excluded from classification as they were younger than 50 years old at disease onset. Rheumatoid factor and anti-cyclic citrullinated polypeptide antibody tests are not routinely obtained in patients with typical disease manifestations of PMR in our centre, and the quality of recorded data for leg pain and duration of morning stiffness varies. As the EULAR/ACR criteria were published in 2012, many of our patients were diagnosed before their dissemination. Furthermore, the EULAR/ACR criteria have been found to have varying sensitivity for PMR in different cohorts [16–18], and are designed for classification rather than diagnostic purposes. In the patients that were classifiable, we found a similar proportion to meet criteria as in the original validation cohort [16]. Our patient cohort and study results emphasise that the diagnosis of PMR should not systematically be disregarded because of a younger patient age at diagnosis – particularly as the disease course appears to be very similar between younger and older patients.

Likewise we can contrast our findings with similar research in giant cell arteritis. PMR and GCA frequently occur together, and there is discussion whether they are part of a spectrum, or two distinct but frequently co-occurring diseases [19]. Apart from their frequent co-occurrence, PET evidence suggests that limited large vessel vasculitis may occur in patients with isolated PMR [20], and histologically normal temporal artery biopsies have shown similarities in cytokine profile between GCA and isolated PMR [21]. A minority of patients with isolated PMR subsequently develops GCA, which may occur years later and despite glucocorticoid therapy [22,23]. Patients diagnosed with GCA at a younger age appear to have a more severe clinical course, with a phenotype that includes predominantly large vessel involvement, a higher risk of aortic complications and more frequent need for intensification of immunosuppression, as compared to older patients who more often develop cranial disease [9]. Interestingly however, presence of PMR symptoms in patients with GCA does not differ based on age.

In summary, our study suggests that isolated PMR is a relatively homogeneous disease with respect to age. Pending further research, more aggressive treatment for younger patients is not warranted.

Disclosures

All authors report no conflicts of interest.

Funding

None.

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