Polypharmacy and comorbidities are not higher at diagnosis in patients with polymyalgia rheumatica compared to osteoarthritis

M.A. Cimmino[1], D. Camellino[2], P.V. Clini[1], M. Cutolo[1,3], E. Hysa[1,4]

[1]Laboratory of Experimental Rheumatology and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova; [2]Division of Rheumatology, La Colletta Hospital, Azienda Sanitaria Locale 3, Arenzano; [3]IRCCS Ospedale Policlinico San Martino, Genova; [4]Department of Experimental Medicine (DIMES), University of Genova, Italy.

Abstract

Objective

Polypharmacy, the prescription of multiple drugs for an individual patient, is increasing in ageing individuals with comorbidities. In polymyalgia rheumatica (PMR), an inflammatory disease of the elderly causing pain and stiffness in the girdles, cardiovascular disease and lymphoproliferative disorders could be increased. Our study evaluated polypharmacy and comorbidities in PMR patients at diagnosis.

Methods

Patients fulfilling the 2012 EULAR/ACR criteria for PMR and sex and age-matched controls with hand osteoarthritis (OA) were evaluated. The Rheumatic Diseases Comorbidity Index (RDCI) was used.

Results

84 PMR patients (mean age 73.4±9 years, 65.1% women) and 84 controls (mean age 72.4±8.2, 65.1% women) were studied. The mean number of drugs assumed by PMR patients was 2.7±2.3 versus 3.1±2.5 of controls (p=0.168). Sixteen PMR patients versus 5 controls had no treatment, 56 versus 67 took 1-5 drugs, and 12 versus 12 >5 drugs (p=0.03). PMR patients with hip pain assumed less drugs (p=0.008) and those with morning stiffness (MS) >45 minutes assumed more drugs (p=0.001). The mean RDCI was 1.56±1.29 in PMR patients and 1.51±1.38 in controls (p=0.62). The number of drugs assumed and RDCI significantly correlated (p<0.001), and both were directly associated with age (p<0.001). At multiple logistic regression, age (p=0.004) and MS (p=0.025) directly, whereas hip pain (p=0.008) and fever (p=0.015) indirectly predicted number of drugs assumed. Age (p<0.001) and white blood cells (p=0.011) directly, whereas fever (p=0.024) indirectly predicted RDCI.

Conclusion

At the time of diagnosis, PMR patients do not show an increased comorbidity index nor number of drugs assumed compared to OA controls.

Key words

polymyalgia rheumatica, hand osteoarthritis, comorbidities, polypharmacy

Marco A. Cimmino, MD
Dario Camellino, MD, PhD
Paolo V. Clini, MD
Maurizio Cutolo, MD
Elvis Hysa, MD

Please address correspondence to:
Marco A. Cimmino
Via Casaregis 2/6
16129 Genova, Italy.
E-mail:
marcoamedeo.cimmino@gmail.com
ORCID iD: 0000-0002-6956-7860

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Introduction

Polypharmacy, the prescription of multiple drugs for an individual patient, is increasing especially in ageing individuals with comorbidities. There is no common agreement on the cut-off for classifying polypharmacy, but the most widely accepted definition is 5 or more medications (1). About half of the patients aged more than 65 years are prescribed 5 or more drugs, a figure that has quadrupled in the last 20 years (2). Ageing of the general population, increased number and awareness of comorbidities, and a shift toward more complex treatments of common diseases may be involved in these changes. In rheumatoid arthritis, polypharmacy is associated with a poor therapeutic response to anti rheumatic drugs and increased risk of serious adverse events (SAEs), with a dose-effect relationship (3). Polymyalgia rheumatica (PMR) is a periarticular inflammatory disease of the elderly causing pain and stiffness in the girdles (4). A recent systematic review showed that cardiovascular disease and lymphoproliferative disorders could be possibly increased in PMR patients, but the uneven quality of the included studies was relatively poor (5). However, population-based studies do not show an increased mortality rate in patients with isolated PMR when compared with the general population of the same age (6). In addition, some comorbidities seen in PMR could not be due to the disease itself, but caused by its treatment. Although polypharmacy and comorbidity indexes are correlated, several studies suggest that they may reflect different features of the patient (3). To our knowledge, the number of drugs administered has not been assessed previously in PMR. Our study is concerned with an evaluation of polypharmacy and comorbidities in PMR patients at diagnosis and their correlation with the disease features.

Methods

Patients were enrolled in this study if they fulfilled the 2012 EULAR/ACR provisional criteria for PMR (7). To avoid the possible effect of treatment with glucocorticoids (GC) on comorbidities, only GC-naïve PMR patients or treated with GC for less than 30 days at the time of the investigation were recruited (8). Sex and age-matched controls were patients with hand osteoarthritis (OA) diagnosed according to the 1990 ACR clinical criteria (9). Both PMR patients and OA controls were consecutively seen in the private practice of a single rheumatologist. Baseline data obtained for PMR patients included demographics, disease duration, BMI, duration of morning stiffness (MS) in minutes, presence of fever, weight loss, sight loss, headache, involvement of the shoulder and pelvic girdles, peripheral arthritis, cranial giant-cell arteritis, C-reactive protein (CRP, mg/L), erythrocyte sedimentation rate (ESR, mm/h), haemoglobin (Hb, g/dL), white blood cell count (WBC), platelets, IgM rheumatoid factor, anti-citrullinated proteins antibodies, assumption of glucocorticoids (GC) before the first visit, GC treatment duration, and GC cumulative dose.

Both groups were interviewed at the time of diagnosis for the number of drugs assumed and for comorbidities by the same investigator. Medication count was calculated by asking the patient to show the list of drugs prescribed by his/her GP and to provide the containers of all drugs assumed. Drugs taken for the index disease were not included in the count. Over-the-counter drugs (OTC) were also recorded, but dietary supplements, topical, herbal, complementary and homeopathic medications were excluded. Polypharmacy was recorded as continuous variable but the number of taken drugs was also stratified in three tiers (0, 1–5, and >5 drugs). The related cut-offs were set on the basis of the literature and the number of medications seen in our study, which ranged between 0 and 9.

Comorbidities were defined as additional, present or past, medical conditions in addition to PMR. The rheumatic diseases comorbidity index (RCDI) was used for counting (10). It was originally developed as self-reported questionnaire asking the patient to indicate up to 11 weighed present or past comorbid conditions, with a range between 0 and 9. The reported comorbidities included pulmonary dis-

eases (asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, pneumonitis, pleuritis), cardiovascular diseases (myocardial infarction, atrial fibrillation, stroke), hypertension, fractures of vertebrae, hip and limbs, depression, diabetes mellitus, cancer, and gastro-intestinal problems including also hepatic diseases. These data were confirmed by the evaluation of medical records and prescribed drugs. To avoid the possibility of including patients with paraneoplastic PMR, those with present cancer were excluded.

This is a non-interventional retrospective study without direct patient intervention, no need of patient consent, or ethical committee approval. Nether the less, due care has been taken for protecting the participants' identity and privacy. Information regarding comorbidity and comedications is part of the routine interview and the patient's consent was not requested. The legal basis for processing personal data is public interest and scientific research (EU General Data Protection Regulation 2016/679 (GDPR), Article 6(1) (e) and Article 9(2)(j); Data Protection Act, Sections 4 and 6).

Frequencies were compared by χ^2 test, means and medians by the Student's t-test and by ANOVA. Correlations were computed with the Pearson's test. Linear logistic regressions with medication count or RDCI as dependent variables were obtained. All calculations were performed with datatab as statistical software (DATAtab e.U., 2023, Graz, Austria).

Results

A total of 84 PMR patients [mean age 73.4±9 years, 55 (65.5%) women] fulfilled the 2012 provisional EULAR/ACR classification criteria and 84 controls affected by hand OA [mean age 72.4±8.2 years, 55 (65.5%) women] fulfilled the ACR classification criteria (p=0.45 for age difference between PMR patients and controls). In PMR patients, median disease duration was two months (0.3–8 months). A total of 41/84 (48.8%) PMR patients had been treated with GC before the first examination; the mean duration of GC treatment was 8.4±11.1 days, and median prednisone dose before assessment was 0 mg (0–750 mg). Data on PMR patients are shown in Table I.

Table I. Characteristics of PMR patients and OA controls.

	PMR	Controls	p-value
Age (years)	73.4 ± 9	72.4 ± 8.2	0.45
BMI	25.6 ± 3.6	24.3 ± 5	0.38
Shoulder involvement (%)	84/84 (100)	NA	-
Hip involvement (%)	65/84 (77.4)	NA	-
Morning stiffness (min)	91 ± 79.3	NA	-
ESR (mm/h)	56.6 ± 24.6	17 ± 14.7	<0.001
CRP (mg/dL)	40.9 ± 27.3	4.4 ± 8.3	<0.001
Haemoglobin (g/L)	12.9 ± 1.4	13.5 ± 1.4	0.009
WBC count (x10^3/μL)	8.5 ± 2.3	5.7 ± 1.4	<0.001
Platelet count (x10^3/μL)	325.6 ± 89.9	238 ± 51.8	<0.001
IgM RF positive (%)	1/84 (1.2)	NA	-
ACPA positive (%)	0/84 (0)	NA	-
Peripheral arthritis (%)	19/84 (22.6)	NA	-
Fever (%)	15/84 (17.9)	NA	-
Weight loss (%)	28/84 (33.3)	NA	-
Headache (%)	2/84 (2.4)	NA	-
Disease duration (months)	2.5 ± 1.6	NA	-
GC treatment at 1st exam (%)	41/84 (48.8)	NA	-
GC therapy duration (days)	8.4 ± 11.1	NA	
GC cumulative dose (mg)	131.1 ± 189.3	NA	-
PDN dose prescribed (mg)	12.9 ± 3.6	NA	-
Prescription of MTX (%)	13/84 (15.5)	NA	-

Data are expressed as mean±standard deviation except for frequencies expressed as percentages (%), NA: not available.

Table II. Number of drugs taken by patients with PMR.

Feature	present	absent	p-value
Hip pain (65)	2.2± 2	4.1±2.6	0.008
Morning stiffness (66)	3.1± 2.3	1.1±1.1	0.001
Peripheral arthritis (19)	2.8± 2.2	2.2±2.5	0.395
Fever (15)	1.9± 2.3	2.8±2.3	0.200
Weight loss (28)	2.8± 2.1	2.6±2.4	0.724
Headache (2)	5.5± 2.1	2.6±2.2	0.294
Methotrexate use (13)	3.6± 2.4	2.5±2.2	0.119

Data are expressed as mean ± standard deviation, according to their disease characteristics. The number of patients presenting the feature is shown in brackets.

The distribution of the number of taken drugs was normal. The mean number of drugs taken by PMR patients was 2.7±2.3 (median 2, range 0–9) in comparison with 3.1±2.5 (median 2.5, range 0–9) of controls (p=0.168). A total of 15/84 (17.9%) PMR patients and 18/84 (21.4%) controls assumed five or more drugs (p=0.56). There were no differences between women and men for number of drugs in the whole group (p=0.62) or in PMR patients (p=0.11). Of all patients, 123 (73.2%) were in the intermediate tier (1–5 drugs assumed), 21 (12.5%) patients were not being treated, and 24 (14.3%) assumed more than five drugs. When PMR patients were compared to controls, 16 *versus* 5 had no treatment, 56 *versus* 67 took 1 to 5 drugs, and 12 *versus* 12 were being treated with more than 5 drugs (p=0.03).

The number of drugs assumed by PMR patients was not correlated with disease duration (p=0.59), duration of GC treatment, if any (p=0.65), GC cumulative dosage (p=0.47) nor with the dose of GC prescribed at first examination (p=0.99). The mean number of drugs according to the individual PMR features is shown in Table II. Patients with pelvic girdle involvement were receiving significantly fewer drugs than the others (p=0.008) and those with MS exceeding 45 minutes received more drugs than those with a shorter duration MS (p=0.001).

Table III. Frequency of the individual comorbidities.

Comorbidity	PMR (n=84)	Controls (n=84)	*p*-value
Pneumological	11 (13.1)	10 (11.9)	0.82
CV events/stroke	19 (22.6)	16 (19)	0.57
Hypertension	45 (53.6)	40 (47.6)	0.44
Fracture	8 (9.5)	7 (8.3)	0.79
Depression	2 (2.4)	5 (6)	0.25
Cancer	13 (15.5)	11 (13.1)	0.66
Diabetes	7 (8.3)	5 (6)	0.55
Gastric	6 (7.1)	15 (17.9)	0.036
RCDI	1.56 ± 1.29	1.51 ±1.38	0.62

Data are expressed as number (%), and RDCI values, expressed as mean ± standard deviation, in PMR patients and controls.

Table IV. The mean RDCI according to the individual PMR features.

Feature	present	absent	*p*-value
Hip pain (65)	1.5±1.4	1.7 ±1.1	0.439
Morning stiffness (66)	1.6±1.3	1.3 ±1.3	0.301
Peripheral arthritis (19)	1.3±1.2	1.7 ±1.3	0.251
Fever (15)	0.9±1	1.7 ±1.3	0.015
Weight loss (28)	1.9±1.2	1.4 ±1.3	0.056
Headache (2)	1.5±0.7	1.6 ±1.3	0.924
Methotrexate use (13)	1.9±1.2	1.5 ±1.3	0.253

Data are expressed as mean ± standard deviation, of patients with PMR according to their disease characteristics. The number of patients presenting the feature is shown in brackets. GCA occurred only in one patient at disease onset.

Table V. Correlations between PMR patients' characteristics and number of drugs assumed or RDCI.

	n. of drugs		RDCI	
	r-value	*p*-value	*r*-value	*p*-value
Age	0.49	<0.001	0.4	<0.001
Weight	-0.06	0.570	-0.04	0.741
Height	0.08	0.466	0.09	0.392
BMI	0.05	0.658	0	0.974
Morning stiffness (min)	0.14	0.195	0.16	0.147
CRP	0.21	0.055	0.11	0.309
ESR	0.18	0.109	0.06	0.609
Haemoglobin	-0.11	0.305	0.09	0.435
WBC	0.02	0.869	0.19	0.089
Platelet count	0.05	0.667	0.06	0.624
PMR duration	0.03	0.804	0.07	0.543
Initial dose of GC	0	0.977	0.08	0.469

The mean RDCI was 1.56±1.29 (median 1, range 0–7) in PMR patients and 1.51±1.38 (median 1, range 0–7) in controls (p=0.62). Men had a higher RDCI (1.83±1.38) than women (1.38±1.29) (p=0.044), but this difference was significant only considering patients and controls together. The single comorbidities determining the RCDI and their different distribution among patients and controls are shown in Table III. Only gastrointestinal problems were significantly more frequent in controls than in PMR patients (p=0.036). RDCI did not correlate with disease duration (p=0.54), duration of GC treatment, if any (p=0.32), GC cumulative dosage (p=0.79) or with dosage of GC prescribed at first examination (p=0.47). The mean RDCI according to the individual PMR features is shown in Table IV. Patients with fever at presentation showed a significantly lower RDCI than the others (p=0.015).

Patients with PMR and cancer were more frequently men (7/13). The tumour types of PMR patients included prostate (3 cases), breast (3 cases), colonic (2 cases), leukemia (2 cases), melanoma (1), rhinopharyngeal (1), and ependymoma (1). Controls with hand OA and cancer were more frequently women (7/11). The types of cancer were breast (4 cases), ovary (2 cases), prostate (2 cases), lymphoma (1), leukaemia (1), melanoma (1), and colonic (1); one patient experienced both prostate and colonic cancer.

By ANOVA, a significant difference was seen in the whole group, for patients with cardiovascular disease (4.1±2.2 *vs*. 2.6±2.1; p<0.001), hypertension (4.1±2.1 *vs*. 1.7±1.7; p<0.001), fractures (4.1±2.8 *vs*. 2.8±2.1; p=0.023), depression (5.3±2.4 *vs*. 2.8±2.2; p=0.003), and diabetes mellitus (4.6±2.8 *vs*. 2.8±2.1; p=0.006) being treated with significantly more drugs. Conversely, there were no differences for the following variables: cancer, respiratory, or gastrointestinal diseases.

The number of drugs assumed and RDCI significantly correlated (r=0.51; p<0.001) in the whole group of patients as well as in PMR (r=0.52; p<0.001). Among PMR features, number of medications and RDCI correlated only with age (p<0.001) (Table V).

At multiple logistic regression, with the number of drugs assumed set as the dependent variable and variables reaching in univariate analysis a p<0.15 as the independent ones, age (p=0.004) and presence of MS (p=0.025) directly; whereas hip pain (p=0.008) and fever (p=0.015) indirectly predicted number of drugs assumed (Supplementary Table S1). With RDCI as dependent variable, age (p<0.001) and WBC count (p=0.011) directly, whereas fever (p=0.024) indirectly predicted it (Suppl. Table S2).

Discussion

To our knowledge, this is the first study considering polypharmacy in PMR. We enrolled a population with early PMR to reduce the interference of long-term GC treatment on comorbidities and related treatments. As a result, the mean duration of GC treatment was only 8.4 days in the subgroup of PMR patients already being treated. Patients with isolated hand OA as controls were chosen with a view to compare PMR with a non-inflammatory disease. Patients

with clinically evident OA of weight-bearing joints, which is known to be associated with many different comorbidities, were not considered.

The mean number of drugs assumed was largely inferior to the cut-off set for polypharmacy, with only 17.9% of PMR patients taking five or more drugs compared with 27.4% in OA. Our results are comparable to those of a European study based on the survey of health, ageing and retirement in Europe on community-based participants aged 65 years or more, where polypharmacy was seen in 26.3% to 39.9% of patients from different countries (11). In Italy, 13.4% of patients aged more than 75 years seen in general practice were on therapy with eight or more drugs (12). Although comparison between studies is difficult because of different definitions of polypharmacy, age groups and settings, the number of drugs administered in our cohort was similar or inferior to that reported in the literature. Although polypharmacy and ageing are associated in general wisdom and in our study, the literature reports contradicting findings. Several studies showed no relationship (12) whereas others showed an almost linear relationship between number of drugs and age (13). In our experience, the mean number of drugs was not different between PMR patients and controls, but the former group more frequently was not receiving medication. This result is consistent with the view that PMR, a disease with a frequently abrupt onset, often occurs in relatively healthy subjects. It is impossible to compare these data with previous data on polypharmacy that are lacking for PMR.

RDCI has been used in several studies in rheumatology (14), for his self-reported questionnaire has the advantage of not including musculoskeletal diseases, a feature that avoids the risk of overadjusting for the index disease. Hypertension was the most prevalent chronic comorbidity as seen in most studies (12), followed by cardiovascular diseases, previous or actual malignancy, and pulmonary diseases. An increased frequency of hypertension has been reported in PMR (15, 16), often preceding disease onset (17, 18). In contrast, we have observed a similar frequency of these diseases in PMR and OA. Only gastrointestinal diseases were significantly more frequent in OA than in PMR patients. This fact, a finding not observed by others (15), may be associated with a higher utilisation of NSAIDs in patients suffering from chronic OA pain. Diabetes frequency was not increased in PMR in our and also in another study (19), although this concept has been contradicted in a recent paper (16). In a study based on administrative databases (15), the prevalence of the different comorbidities was similar between PMR patients and controls, although the huge number of patients involved highlighted also minor differences of little biological importance. The possibility that patients diagnosed with PMR more than others are extensively studied to exclude cancer, infections or other autoimmune diseases in accordance with current clinical classification criteria should be considered. This fact could lead to a factitious decrease in the computation of these comorbidities. We believe, however, that the short interval between onset of symptoms and specialist consultation should have avoided this bias.

When the number of drugs was correlated with PMR features, patients with pelvic girdle involvement were taking significantly fewer drugs than the others (p=0.008); those with MS exceeding 45 minutes were being treated with significantly more drugs than those with a shorter duration of MS (p=0.001). These findings were confirmed by multiple logistic regression, where also age was found predictive of drug consumption, whereas fever was a protective feature. Pelvic girdle involvement and fever are likely a sign of poor prognosis PMR (19). In RA patients, the correlation between polypharmacy and prolonged MS has not been investigated. We hypothesise that if PMR patients are generally healthier at baseline, those presenting with more intense and widespread disease manifestations, such as pelvic girdle involvement and fever, might represent an even healthier subset. The presence of pelvic symptoms, which reflects a more extensive inflammatory involvement, could indicate a robust inflammatory response, more likely to develop in patients without significant comorbidities or conditions of frailty, who therefore require fewer concomitant medications. Conversely, prolonged MS, while a diagnostic hallmark of PMR, may not be exclusively due to inflammatory disease activity. Longer MS duration could also be influenced by coexisting degenerative or musculoskeletal conditions common in elderly patients (such as osteoarthritis, sarcopenia, or frailty syndromes), potentially leading to earlier pharmacological interventions and to an increased burden of polypharmacy.

When RDCI and PMR features were correlated, patients with fever at presentation showed a significantly lower RDCI than the others (p=0.015). This feature was confirmed at multiple logistic regression, together with the observation that age and WBC predicted comorbidities. In conclusion, PMR patients with onset characterised by fever have less comorbidities and were being treated with fewer drugs, an observation that might be due to patients with multiple comorbidities often having a compromised immune system, either from the diseases themselves or as a side effect of their treatment. This low-grade chronic inflammation or immune suppression could potentially alter the ability to mount a fever response.

We believe that a strong point of our study is its setting in a private practice, where patients with PMR are usually seen within a brief period from disease onset, irrespective of their disease severity. In contrast, patients seen in tertiary referral centres are more frequently affected by severe PMR. In addition, patients and controls were seen by the same rheumatologist, a fact that assures consistency in diagnosis and evaluation. On the other hand, however, drawing general conclusions from these data could be hindered by the relatively small sample and by the limited source area of the patient sample. The concurrent evaluation of drug consumption and comorbidities was a further strong point. Medications were assessed by evaluating the list of drugs in the GP's report and checking the drug containers, which we believe increased accura-

cy. In addition, OTC medications were included in the count. However, dietary supplements, topical, herbal, complementary and homeopathic medications were not assessed because they were taken without medical consultation and scarce pharmacological effect. The weak point of this study is the relatively small number of patients and the fact that only number, but not type, of drugs was recorded.

In conclusion, PMR patients are not affected by a higher number of comorbid conditions, nor assume more drugs than those with hand OA. On the contrary, they are significantly more frequently untreated. This is different from the common assumption of PMR as a disease with many comorbidities (15, 20).

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