Subjective sleep disturbances at the time of diagnosis in patients with polymyalgia rheumatica and in patients with seronegative elderly-onset rheumatoid arthritis. A pilot study

Ciro Manzo¹, Alberto Castagna²

¹Internal and Geriatric Medicine Department, Azienda Sanitaria Locale Napoli 3 Sud, Rheumatologic Outpatient Clinic Hospital "Mariano Lauro", Sant’Angelo, Italy
²Geriatric Medicine Department Azienda Sanitaria Provinciale Catanzaro, Fragility Outpatient Clinic, Casa della Salute di Chiaravalle Centrale, Catanzaro, Italy

Abstract

Objectives: To investigate subjective sleep disturbances in patients with recent-onset polymyalgia rheumatica (PMR) and in patients with recent-onset seronegative elderly-onset rheumatoid arthritis (SEORA).

Material and methods: The study involved patients consecutively referred to two outpatient clinics from January to June 2018, with a diagnosis of PMR according to 2012 European League Against Rheumatism and American College of Rheumatology provisional criteria, and patients with a diagnosis of SEORA according to 1987 American Rheumatism Association criteria + age + absence of rheumatoid factor and anti-citrullinated peptide antibodies. All patients were naive to glucocorticoid (GC) therapy. After informed consent, we asked the patients to fill out a questionnaire including the Medical Outcomes Study – Sleep Scale (MOS-SS), pain Visual Analogic Scale (VAS), Cumulative Illness Rating Scale (CIRS), Neuropsychiatric Inventory (NPI), and how many minutes their morning stiffness (MS) lasted, at baseline and after 1 (T1) and 12 (T2) months. Differences between groups were calculated with the t-test; all p-values were two-sided and p < 0.05 was used to determine statistical significance. The study was approved by the local ethics committee and carried out in accordance with the Helsinki Declaration.

Results: The MOS-SS scores and MS duration were the only variables to show at T0 a significant difference between the two groups. In particular, MOS-SS scores were 47.6 ±8.4 (PMR) and 28.26 ±12.4 (SEORA), with p-values = 0.000. The MS duration was 90 ±9.9 minutes and 45 ±5.5 minutes, with p-value = 0.000. At T1 and T2, MOS-SS scores and MS duration decreased in the two groups, and no significant differences were found.

Conclusions: The study suggests that the assessment of subjective sleep disturbances can be useful in the differential diagnosis between recent-onset PMR and SEORA.

Key words: polymyalgia rheumatica, subjective sleep disturbances, elderly-onset seronegative rheumatoid arthritis.

Introduction

Polymyalgia rheumatica (PMR) and seronegative elderly-onset rheumatoid arthritis (SEORA) are two of older adults’ most common inflammatory rheumatic diseases [1, 2]. At their first presentation, there are many similarities between PMR and SEORA so that they were considered the same disease or as two different aspects of the same nosographic entity [3]. Moreover, it should...
not be ruled out in clinical practice that patients initially diagnosed with PMR might be reclassified as having a different disease during their follow-ups [4].

In addition to the involvement of the shoulder girdle, common findings are morning stiffness longer than 45 minutes, raised erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) concentrations, and a good response to low doses of glucocorticoids (GCs) [5–7]. Nevertheless, in patients with PMR, GCs are used for several months and in some cases throughout life. In contrast, in patients with SEORA, short-term treatment should be considered only when initiating or changing disease-modifying anti-rheumatic drugs, followed by prednisone tapering [8].

In PMR, sleep disorders have rarely been assessed, even if patients report them [9–11].

In patients with RA, correlations between sleep disorders and pain, mood disorders and GC therapy have been investigated more frequently than the relationship between sleep quality and disease activity (which is still controversial) [12–17]. However, in patients with SEORA data are very scarce and these correlations are much less clear.

To our best knowledge, no data are available in the literature about the usefulness of the assessment of subjective sleep disturbances in the differential diagnosis between PMR and SEORA patients at the time of diagnosis.

Material and methods

Study design

It is an observational case-case study.

Objectives

To evaluate whether the assessment of subjective sleep disorders shows differences between patients with PMR and those with SEORA, at the time of diagnosis and in the absence of GC therapy.

To assess whether these differences relate to some factors such as CRP concentrations, co-morbidities, morning stiffness duration, and mood disorders such as depression and anxiety.

Setting and participants

We approached all the patients consecutively referred to two bi-centric outpatient clinics from January to June 2018, with clinical, laboratory and instrumental findings consistent with a diagnosis of PMR or SEORA. Polymyalgia rheumatica was diagnosed according to 2012 European League Against Rheumatism and American College of Rheumatology (EULAR/ACR) [11]. Seronegative elderly-onset rheumatoid arthritis was diagnosed in patients older than 60 years without rheumatoid factor (RF) and/or anti-citrullinated peptide antibodies (ACPA) according to the criteria proposed by the American Rheumatism Association (ARA) in 1987 [18].

Exclusion criteria were:

- malignancy,
- body mass index (BMI) > 30 kg/m²,
- intake in the previous month of GCs and/or of drugs used to treat sleep disturbance or that could favor sleep disturbances [19, 20].

Routine laboratory tests such as blood urea nitrogen, complete blood count; liver function tests, creatinine, ESR, CRP concentrations, fecal immunochemical occult blood test and measurement of fecal calprotectin were assessed. The patients with abnormal values were evaluated for further, more in-depth diagnostic investigations.

After informed consent, we asked the patients to fill out a questionnaire including the Medical Outcomes Study – Sleep Scale (MOS-SS), pain Visual Analogic Scale (VAS), Cumulative Illness Rating Scale (CIRS), Neuropsychiatric Inventory (NPI), and duration (minutes) of morning stiffness (MS). Some socio-demographic data, such as age and sex, were also included in the questionnaire. After the first visit (T0), all patients began therapy with a standardized dose (12.5–15 mg/day) of prednisone, and were submitted to a new clinical and laboratory evaluation after one month (T1) and after 12 months (T2). On those occasions, all patients re-filled in the same questionnaire. Patients who changed the first diagnosis during follow-ups were excluded.

Data sources and methods of assessment

The MOS-SS is a 12-item questionnaire evaluating sleep quality and quantity, with a score between 12 and 71. No formal cut-off scores are provided. It is divided into 6 dimensions evaluating “sleep disturbance”, “snoring”, “sleep awakening short of breath or with headache”, “sleep adequacy”, “somnolence”, and “quantity of sleep/optimal sleep”. A sleep problems index summarizes information across the 9-item MOS-SS. Higher scores indicate greater sleep impairment [21]. The MOS-SS psychometric properties have been evaluated in patients with a variety of conditions characterized by pain; in particular, it is considered the best choice in assessing sleep impairment due to pain [22, 23]. Additionally, it showed good validity, reliability and sensitivity to change in two studies involving RA patients [14, 24].

The VAS was used for assessing pain, with 0 points standing for no pain and 10 points for maximum pain.
Depression and anxiety were assessed using the NPI, with 0 points for absent and 3 points for severe [25]. Although the NPI was developed to assess dementia-related behavioral and psychological disturbances, it was also validated in the assessment of psychological changes in non-dementia patients [26].

The CIRS quantifies the burden of disease in elderly patients, through 14 blocks of organ involvement, with a score between zero (no problem) and three (marked problem). High scores indicate higher severity. Its maximum score is 56 points [27].

The classification criteria proposed by the ARA in 1987 were preferred to the 2010 ACR/EULAR classification criteria. As several researchers highlighted, 2010 ACR/EULAR classification criteria have a specificity lower than 1987 ACR criteria, classifying about 50% of patients (especially if older than 60 years) with non-RA diagnoses as having RA [28, 29]. Taking into account that SEORA is the most frequent PMR-mimicking disease, the low specificity of 2010 EULAR/ACR criteria could have been misleading.

### Study size

Based on our unpublished data, it was calculated that 20 patients affected by PMR and 33 patients affected by SEORA had to be recruited to have 95% power with a 5% type 1 error level to detect a minimum clinically significant difference.

### Statistical analysis

Descriptive statistics were recorded for each variable, with the quantitative variables shown as mean values and standard deviation. In the population, we considered the variables showing a normal distribution. Indeed, the asymmetry in the evaluated variables was between -2 and +2, and the median practically coincided with the mean. The Anderson-Darling test also confirmed the data (possibly normal; \(\alpha = 0.05\)). Differences between groups were calculated with the \(t\)-test. All \(p\)-values were two-sided and a \(p\)-value < 0.05 was considered as statistically significant. Data analysis was performed using SPSS Statistics for Windows version 23 software (SPSS Inc., Chicago, IL, USA).

### Ethical approval

The study was approved by the local Ethical Committee (number: 05.2018) and carried out in accordance with the Helsinki Declaration, revised in 2013.

### Results

The main demographic data and medical records of enrolled patients are listed in Table I. In Table II, we reported MOS-SS scores, pain VAS, CRP concentrations, and MS duration at T0, T1, and T2. The MOS-SS scores and MS were the only vari-
enables to show at T0 a significant difference between the two cohorts. In particular, MOS-SS scores were 47.6 ±8.4 in the PMR cohort and 28.26 ±12.4 in the SEORA one, with p-values = 0.000. Morning stiffness duration was 90 ±9.9 minutes in PMR and 45 ±5.5 minutes in SEORA, with p-value = 0.000. At T1 and T2, MOS-SS scores and MS duration decreased in the two groups, and we did not find significant differences at the end of the study.

Discussion

Some confounding factors must be taken into account in assessing subjective sleep disturbances in patients with PMR or SEORA. For instance, they have been related to mood disorders, such as depression and anxiety [5]. A higher prevalence of depressive and anxiety symptoms was evident in RA patients compared to the normal population [30, 31]. Depression is also common in patients with PMR [10]. In our study, we found no correlation between sleep disorders and anxiety or depression. Indeed, NPI scores were identical in the two groups at both T0 and T1 and T2.

Other significant confounding factors, such as intake of prednisone and/or drugs used to treat or that could favor sleep disturbances in the previous month, were exclusion criteria.

Glucocorticoids given to the patients were clinically effective. After one-month therapy with a standardized dose (12.5–15 mg/day) of prednisone, MOS-SS scores significantly improved in the two groups, focusing the attention on the relationship between sleep disturbances, immunity and inflammation. This relationship is complex and unclear in many respects [32, 33]. For instance, some researchers highlighted that in patients affected by moderately or severely active RA treated with interleukin 6 (IL-6) receptor antagonist tocilizumab, sleep quality improved significantly at first-month assessment compared to baseline. This observation could suggest that IL-6 has a relevant role in the sleep impairment of RA patients [34].

Nevertheless, other biological disease-modifying anti-rheumatic drugs that are not specifically active towards this cytokine have a similar positive impact on sleep quality in patients with RA [35, 36]. Unfortunately, we did not assess serum concentrations of IL-6. However, it is common knowledge that IL-6 plays a central role in the hepatic production of CRP and CRP concentrations were not significantly different in our patients at T0, T1 and T2.

Morning stiffness duration is another discussion point. In PMR, MS is a generally accepted core symptom with a greater decision-making impact (two points) in comparison to RA (one point) [4, 11, 18, 37, 38]. In our study, MS was significantly longer at baseline in patients affected by PMR than in those affected by SEORA (90.9 ±9.9 vs. 45.0 ±5.5; p-value = 0.000), whereas we did not find a statistically significant difference in CRP concentrations in the two groups (26.4 ±8.2 vs. 24.0 ±6.0 mg/dl; p-value = not significant). The relationship between MS and sleep impairment is bi-directional, with inflammation as only one of the involved factors. The abrupt onset of PMR during nighttime rest that is much more frequent in PMR patients than in SEORA patients and the possible role of other, different inflammation mediators can explain the discrepancy between MS and CRP concentrations [39].

Finally, we did not find a statistically significant difference in CRP concentrations in the two groups. In Table II, we did not list ESR values. It is common knowledge that in a proportion of PMR patients – from 7 up to 22% – ESR is not raised at the time of diagnosis [40, 41]. Moreover, ESR can depend on several variables, whereas this does not happen with CRP concentrations [42]. For these reasons, we choose to assess only CRP concentrations.

Strengths and limitations

The study design seems to be its main strength. On the other hand, lack of some laboratory findings (such as IL-6 serum concentrations), and of assessment of objective sleep disorders (through polysomnography, for example) could be considered as limitations.

Conclusions

Our pilot study suggests that the assessment of subjective sleep disturbances can be useful in the differential diagnosis between newly diagnosed PMR and newly diagnosed SEORA.

To date, the reasons why PMR patients have higher MOS-SS scores at the time of diagnosis remain speculative, and should inform future appropriately designed studies.

The authors declare no conflict of interest.

References

1. Chuang T-Y, Hunder GG, Ilstrup DM, Kurland LT. Polymyalgia rheumatica: a 10-year epidemiologic and clinical study. Ann Intern Med 1982; 97: 672-680, DOI: 10.7326/0003-4819-97-5-672.
2. Laiho K, Tuomilehto J, Tilvis R. Prevalence of rheumatoid arthritis and musculoskeletal diseases in the elderly population. Rheumatol Int 2001; 20: 85-87, DOI: 10.1007/s002960000087.
3. Healey LA. Polymyalgia rheumatica and seronegative rheumatoid arthritis may be the same entity. J Rheumatol 1992; 19: 270-272.
4. Manzo C, Camellino D. Polymyalgia rheumatica: diagnostic and therapeutic issues of an apparently straightforward disease. Recenti Prog Med 2017; 108: 221-231, DOI: 10.1701/2695.27559.

5. Manzo C, Natale M, Traini E. Diagnosis of polymyalgia rheumatica in primary health care: favoring and confounding factors – a cohort study. Reumatologia 2018; 56: 131-139, DOI: 10.5114/reum.2018.76900

6. Manzo C, Emamifar A. Polymyalgia rheumatica and seronegative elderly-onset rheumatoid arthritis: two different diseases with many similarities. EMJ 2019; 4: 111-119.

7. Caporal R, Montecucco C, Epis O, et al. Presenting features of polymyalgia rheumatica (PMR) and rheumatoid arthritis with PMR-like onset: a prospective study. Ann Rheum Dis 2001; 60: 1021-1024, DOI: 10.1093/ard/60.11.1021.

8. Olivieri I, Palazzi C, Peruz G, Padula A. Management issues with elderly-onset rheumatoid arthritis: an update. Drugs Aging 2005; 22: 809-822, DOI: 10.2165/00002512-200522100-00002.

9. Mackie SL, Twohig H, Neill LM, et al. The OMERACT core domain set for outcome measures for clinical trials in polymyalgia rheumatica. J Rheumatol 2017; 44: 1515-1521, DOI: 10.3899/jrheum.161109.

10. Vivekanantham A, Blagojevic-Bucknall M, Clarkson K, et al. How common is depression in patients with polymyalgia rheumatica? Clin Rheumatol 2018; 37: 1633-1638, DOI: 10.1007/s10067-017-3691-9.

11. Dasgupta B, Cimmino MA, Kremers HM, et al. 2012 Provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Arthritis Rheum 2012; 64: 943-954, DOI: 10.1002/art.34356.

12. Coskun Benlidayi I. Sleep impairment: an obstacle to achieve optimal quality of life in rheumatoid arthritis. Rheumatol Int 2018; 38: 2183-2192, DOI: 10.1007/s10067-017-3691-9.

13. Purabdollah M, Lakdizaji S, Rahmani A. Relationship between sleep, pain and inflammatory markers in patients with rheumatoid arthritis. J Caring Sci 2017; 6: 249-255, DOI: 10.15171/jcs.2017.024.

14. Grabovac I, Haider S, Berner C, et al. Sleep quality in patients with rheumatoid arthritis and association with pain, disability, disease duration, and activity. J Clin Med 2018; 7: 336, DOI: 10.3390/jcm70033.

15. Luyster FS, Chasens ER, Wasko MC, Dunbar-Jacob J. Sleep quality and functional disability in patients with rheumatoid arthritis. Clin Rheumatol 2011; 7: 49-55.

16. Loppenthun K, Esbenshade BA, Jemmum P, et al. Sleep quality and correlates of poor sleep in patients with rheumatoid arthritis. Clin Rheumatol 2015; 34: 2029-2039, DOI: 10.1007/s10067-015-2875-4.

17. Drewes AM, Nielsen KD, Hansen B, et al. A longitudinal study of clinical symptoms and sleep parameters in rheumatoid arthritis. Rheumatology (Oxford) 2000; 39: 1287-1289, DOI: 10.1093/rheumatology/39.11.1287.

18. Amett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31: 315-324, DOI: 10.1002/art.1780310302.
34. Fragiadaki K, Tektonidou MG, Konsta M, et al. Sleep disturbances and interleukin 6 receptor inhibition in rheumatoid arthritis. J Rheumatol 2012; 39: 60-62, DOI: 10.3899/jrheum.110617.
35. Wells G, Li T, Tugwell P. Investigation into the impact of abatacept on sleep quality in patients with rheumatoid arthritis, and the validity of the MOS-Sleep questionnaire Sleep Disturbance Scale. Ann Rheum Dis 2010; 69: 1768-1773, DOI: 10.1136/ard.2009.119727.
36. Zamarrón C, Maceiras F, Mera A, Gómez-Reino JJ. Effect of the first infliximab infusion on sleep and alertness in patients with active rheumatoid arthritis. Ann Rheum Dis 2004; 63: 88-90, DOI: 10.1136/ard.2003.007831.
37. Bird HA, Leeb BF, Montecucco CM, et al. A comparison of the sensitivity of diagnostic criteria for polymyalgia rheumatica. Ann Rheum Dis 2005; 64: 626-629, DOI: 10.1136/ard.2004.025296.
38. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010; 62: 2569-2581, DOI: 10.1002/art.27584.
39. Galbo H, Lisbeth K. Circadian variations in clinical symptoms and concentrations of inflammatory cytokines, melatonin, and cortisol in polymyalgia rheumatic before and during prednisolone treatment: a controlled, observational, clinical experimental study. Arthritis Res Ther 2016; 18: 174, DOI:10.1186/s13075-016-1072-4.
40. Ellis ME, Ralston S. The ESR in the diagnosis and management of the polymyalgia rheumatica/giant cell arteritis syndrome. Ann Rheum Dis 1983; 42: 168-170, DOI: 10.1136/ard.42.2.168.
41. Sobrero A, Manzo C, Stimamiglio A. The role of the general practitioner and the out-of-hospital rheumatologist in the diagnosis and follow-up of patients with polymyalgia rheumatica. Reumatismo 2018; 70: 44-50, DOI: 10.4081/reumatismo.2018.1036.
42. Çayakar A. Sedimantasyon & CRP; Geçmişten Geleceğe. Aegean J Med Sci 2019; 2: 84-95, DOI: 10.33713/ejetbd.548235.