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Article

Sleep impairment at the time of first diagnosis in patients with seronegative elderly-onset rheumatoid arthritis and in patients with polymyalgia rheumatica

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Abstract: **Background**: Differential diagnosis between polymyalgia rheumatica (PMR) and seronegative elderly-onset rheumatoid arthritis (SEORA) is not easy, to the point that in the past they were considered the same entity. In these patients, sleep disorders have been scarcely assessed, and considered as expression of mood disorders such as depression and anxiety. **Methods**: In 38 Caucasian elderly patients (median age: 73.9 ± 8.06 years) consecutively referred to two outpatient clinics from January to May 2018 with diagnosis of PMR and SEORA, sleep impairment was assessed using the Medical Outcomes Study-Sleep scale (MOS-SS). Depression and anxiety were assessed using the Neuropsychiatric Inventory (NPI) score, with point 0 for absent and point 3 for severe. Comorbidities were assessed using the Cumulative Illness Rating Scale (CIRS). Patients taking medications used to treat sleep disturbance or that could favor sleep disturbances were excluded. The study was approved by the local ethics committee and carried out in accordance with the Helsinki Declaration, revised 2013. Every patient signed an informed consent form at the time of the first visit. **Results**: MOS-SS total point in PMR patients was significantly higher than in SEORA patients (47.60 ± 8.4 vs 28.26 ± 12.4; P = 0.000). After six-month therapy with prednisone (12.5–15 mg/day, followed after 4 weeks by gradual tapering), MOS-SS total point improved in the two groups of patients, with no significant difference (17.0 ± 6.2 vs 17.8 ± 4.2; P = 0.644). No correlation was found between MOS-SS and comorbidities, and between MOS-SS, anxiety or depression. **Conclusions**: Our data suggest that the assessment of sleep impairment could be very useful in the differential diagnosis between PMR and SEORA. Up today, the reasons why patients with PMR have—at the time of diagnosis—a sleep impairment higher than SEORA are speculative. Further ad hoc complementary studies in multicenter cohorts are needed.

Keywords: Polymyalgia rheumatica; elderly-onset rheumatoid arthritis; sleep impairment; seronegative rheumatoid arthritis; elderly patients

1. Introduction

Polymyalgia rheumatica (PMR) and seronegative elderly-onset rheumatoid arthritis (SEORA) are two of the most frequent inflammatory rheumatologic diseases in the elderly patient [1,2]. At first presentation there are many similarities between PMR and SEORA which may lead to a real diagnostic conundrum. Differential diagnosis between these diseases is not easy, to the point that they have been considered as the same entity or as two components of a single disease process [3-6]. In patients with PMR or SEORA, sleep impairment has been scarcely assessed [7-9], and considered as expression of mood disorders [10-12].

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2. Matherials and Methods

We assessed, using the Medical Outcomes Study - Sleep Scale (MOS-SS), the sleep impairment in all patients affected by PMR or SEORA, consecutively referred to our outpatient clinics from January to May 2018. MOS-SS is a 12-item questionnaire evaluating sleep quality and quantity, with total score among 0 and 100. Higher scores indicate greater sleep impairment [13]. MOS-SS is considered the first choice in assessing the sleep impairment due to pain [14,15]. For diagnosis of PMR, we used the criteria proposed by Healey [16] complemented by the classification criteria proposed in 2012 by European League Against Rheumatism and American College of Rheumatology collaborative group [17]. Diagnosis of RA was made according to the criteria proposed in 1987 by American Rheumatism Association [18]. Diagnosis of SEORA was made when RA developed in patients older than 60 years, and FR and ACPA were absent.

Depression and anxiety were assessed using the Neuropsychiatric Inventory (NPI) score, with point 0 for absent and point 3 for severe. Even if NPI was developed to assess dementia-related behavioral and psychological disturbances, it also proved in the assessment of psychological changes in non-dementia patients [19,20]. Finally, co-morbidities were assessed using the Cumulative Illness Rating Scale (CIRS) by Parmelee *et al* [21]. Patients taking medications used to treat sleep disturbance or that could favor sleep disturbances [22] were excluded.

All data analysis was completed using SPSS Statistics Version 23 (SPSS Inc., Chicago, IL, USA). Continuous variables were assessed for normality, and non-parametric tests were used where appropriate. All p-values were two-sided and $p < 0.05$ was used to indicate the statistically significant.

The study was approved by the local ethics committee and carried out in accordance with the Helsinki Declaration, revised 2013. Every patient signed an informed consent form at the time of the first visit.

3. Results

Our bi-centric cohort was of 38 patients, 19 affected by PMR (group A) and 19 affected by SEORA (group B). All patients were Caucasian, with F/M equal to 29:9. Their age range was of 61-100 years (mean 73.9 years and SD 8.06); CIRS was 27.9 (SD 4.9) ; NPI was 6.0 (SD 5.3), with scores for depression and anxiety < 1. ***Table 1*** shows the main demographic data and medical records.

Table 1. : Demographic and medical data of our patients.

Demographics	
Female/male (n)	29/9
Age at first diagnosis (years-old)	61-100
Medical records	
RF (normal range)	38/38
ACPA (normal range)	38/38
ESR (median)	59 +- 10.6
CRP concentration (median)	26.4 +- 8.2
CIRS (median)	27.9 +- 4.9
NPI total point (median)	6.0 +- 5.3

ESR = erythrocyte sedimentation rate ; CRP = C-reactive protein ; RF = rheumatoid factor ; ACPA = anti-citrullinated peptide antibodies.

After six months of therapy with prednisone (12.5-15 mg/day at the time of first visit, followed by gradual tapering) all 38 patients had been re-assessed. In patients with diagnosis of SEORA, disease modifying anti-rheumatic drugs (DMARDs) were not used. We found that at the time of diagnosis (T0), MSS-SS total points were significantly higher in patients with PMR (47.60 +- 8.4 vs

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28.26 +- 12.4 ; P = 0,000). No differences were present in CIRS and in NPI scores. After six months (T1), MOS-SS total points overlapped in the two groups (17.0 +- 6.2 in group A vs 17.8 +- 4.2 in group B; P = 0,644) (Table 2). CIRS and NPI scores were unchanged

Table 2. MOS-SS total points in PMR and in SEORA patients, at the time of first diagnosis (TO) and after six-month of prednisone therapy (T1).

	PMR MOS-SS	SEORA MOS-SS	P
T0	47,60±8,40	28,26±12,4	0,000
T1	17,00±6,20	17,80±4,20	0.644

4. Discussion

SEORA is the most enigmatic and frequent PMR-mimicking disease. At first presentation, there are many similarities between these two diseases: in addition to the acute involvement of the shoulder joints, characterisitic features of both diseases are morning stiffness longer than 45 minutes, raised erythrocyte sedimentation rate (ESR), and a good response to low doses of prednisone [3,7]. A correct diagnosis has relevant therapeutic implications. In patients with PMR, systemic glucocorticoids (GCs) are used for several months and in some patients throughout life, and their side effects can induce significant comorbidities. On the contrary, in patients with SEORA, short term treatment with GCs should be considered only when initiating or changing DMARDs, followed by rapid tapering [24].

According our best knowledge, this is the first report that evaluated sleep impairment in the differential diagnosis between PMR and SEORA. Our data suggest that the assessment of sleep impairment could be useful in the differential diagnosis. Up today, in absence of a specific diagnostic test, the diagnosis of PMR remains basically clinical. Even if it is not a specific diagnostic test, the assessment of sleep impairment could represent a new measurable parameter of evaluation.

Higher prevalence of depressive and anxiety symptoms was highlighted in early arthritis patients in comparison to the normal population [25,26]. Similarly, anxiety and depression are present in patients with PMR [27] even if they seem less assessed as patient-reported outcomes [28]. When evaluated, sleep impairment in patients with PMR or SEORA was considered as a consequence of these mood disorders. We found no correlation between sleep impairment and anxiety or depression. As highlighted, we excluded patients taking medications used to treat sleep disturbance or that could favor sleep disturbances. On the other hand, we found that after therapy with prednisone, MOS-SS total points significantly improved in the two groups of patients. This observation focused the attention on the relationship between sleep impairment and inflammation. It is known that human health and immunity are linked to a circadian clock in the suprachiasmatic nucleus (SCN) [29,30]. Both in PMR and in SEORA a circadian pattern in cytokine production (including interleukin 6 [IL-6]) is present, with higher levels in PMR than in SEORA. [31,32]. A different impairment of the hypothalamic-pituitary- adrenal axis in the pathogenesis of PMR and SEORA has been proposed [33], and could explain the difference in sleep impairment. Finally, the classical onset of PMR during night-time rest could account for greater sleep impairment in these patients. In PMR, morning stiffness is generally accepted core symptoms, as reflected by the various sets of criteria defined for its diagnosis [32].

Our study has some limits. First of all, our cohort had a poor numerical consistency, and this made difficult (or not possible) some statistical evaluations such as power analyze. Certainly, our exclusion criterion contributed to reduce the number of the enrolled patients, since drugs used to treat sleep disturbance or that could favor sleep disturbances are common among the elderly. Secondly, some laboratory or instrumental data were absent and so we cannot demonstrate our working-hypotheses. Further ad hoc complementary studies in multicenter cohorts are needed. Finally, the duration of our follow-ups may not exclude a diagnostic change from PMR to SEORA. We know that up to 20-30 % of patients changed the first diagnosis of PMR in SEORA during

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follow-ups and that in some patients this change can realize also after one year [4, 34-37]. The aim of our study was to evaluate if the assessment of sleep impairment was useful in the differential diagnosis between PMR and SEORA at the time of their first diagnosis.

5. Conclusions

Our data highlighted that at the time of first diagnosis, MSS-SS total points were significantly higher in patients with PMR than in patients with SEORA. Therefore, the assessment of sleep disturbances can be useful in distinguishing these two similar inflammatory rheumatic diseases. Further studies in multicenter cohorts are needed.

Conflicts of Interest: The Authors declare no conflict of interest.

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