Sleep Disturbances and Prevalence of Depression in Systemic Lupus Erythematosus Patients Receiving Intravenous Cyclophosphamide

Alterações do Sono e Prevalência de Depressão em Pacientes Lúpicos em Uso de Pulsoterapia com Ciclofosfamida

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ABSTRACT

Background: *Pulse i.v. cyclophosphamide is a therapeutic option in severe forms of systemic lupus erythematosus (SLE). However, the overall toxicity and risk profile are yet to be adequately defined.* ***Objective:*** *To evaluate the occurrence of sleep disturbances in SLE patients subjected to i.v. cyclophosphamide.* ***Methods:*** *We studied thirty consecutive SLE patients (27 female) age range 14 to 53 years (mean 30.5 ± 10 years) that received i.v. cyclophosphamide (mg) (mean 948.27 ± 221.39). Depressive symptoms, quality of sleep, and the presence of excessive daytime sleepiness were evaluated. Disease severity was assessed by the SLEDAI. Quality of sleep was assessed by the Pittsburgh Sleep Quality Index (PSQI) and excessive daytime sleepiness (EDS) by the Epworth Sleepiness Scale (ESS). Depressive symptoms were evaluated using the 21-item Beck Depression Inventory (BDI).* ***Results:*** *SLEDAI values ranged from 2 to 46 (mean 17 ± 11.4). The most common comorbidities were systemic arterial hypertension (30%), anemia (23.3%), osteoporosis (23.3%), and cardiomyopathy (6.6%). Seizures occurred in one patient (3.3%). Poor quality of sleep (PSQI ≥ 6) and EDS (ESS >10) were found in 66.7% and 30% of the patients, respectively. Depressive symptoms (BDI >19) were present in 40% of the patients and were associated with poor sleep quality (P = 0.03).* ***Conclusions:*** *Our findings show an increased prevalence of poor sleep quality and depressive symptoms in SLE patients receiving pulse i.v. cyclophosphamide. These findings were similar to other previously reported series of SLE patients regardless of the therapies used.*

Keywords: *lupus, sleep, cyclophosphamide, SLEDAI, hypersomnolence, depression.*

RESUMO

Introdução: O uso de ciclofosfamida endovenosa é uma opção terapêutica nas formas graves de lúpus eritematoso sistêmico (LES). No entanto, a toxicidade e o perfil de risco ainda não estão adequadamente definidos. **Objetivo:** Avaliar sobre a ocorrência de alterações do sono em pacientes portadores de LES submetidos à terapia com ciclofosfamida endovenosa**. Métodos:** Nós estudamos 30 casos consecutivos (27 do sexo feminino) com idade entre 14 e 53 anos (30,5 ± 10), em pulsoterapia com ciclofosfamida (mg) (média 948,27 ± 221,39). Os pacientes foram avaliados quanto à presença de sintomas depressivos, qualidade do sono e sonolência excessiva diurna (SED). A qualidade do sono foi estudada pelo índice de qualidade do sono de Pittsburgh (IQSP), a SED pela escala de sonolência de Epworth e os sintomas depressivos pelo Inventário de Depressão de Beck (21 itens). A gravidade da doença foi avaliada por intermédio do SLEDAI. **Resultados:** O SLEDAI oscilou entre 2 e 46 (17 ± 11,4). Hipertensão (30%), anemia (23,3%), osteoporose (23,3%) e miocardiopatia (6,6%) foram as comorbidades mais observadas. Um paciente tinha história de convulsões (3,3%). Má qualidade do sono (PSQI ≥ 6) foi encontrada em 66,7% e SED (ESS > 10), em 30% dos pacientes. Sintomas de depressão (BDI > 19) estavam presentes em 40% dos casos. Os sintomas depressivos associaram-se à presença de má qualidade do sono (p = 0,03). **Conclusões:** Nosso estudo mostra que alterações do sono e sintomas depressivos são comuns em pacientes portadores de LES em pulsoterapia com ciclofosfamida. Esses achados são similares a outros estudos previamente relatados e são independentes do tipo de tratamento utilizado.

Palavras-chave: lúpus, sono, ciclofosfamida, SLEDAI, sonolência diurna, depressão.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by autoantibody production presenting with a wide spectrum of clinical manifestations and oscillating in an unpredictable flare-and-remit way[1]. Nervous system manifestations can occur at any time during the course of the disease and are usually associated to poor prognosis[2,3]. Disturbed sleep has been reported to be common in SLE and medications can further interfere on sleep[4,5]. Nocturnal episodes of pain, of various origins, associated or not with neurovegetative symptoms, such as breathlessness, sweating, and palpitation, may be associated with sleep fragmentation and excessive daytime sleepiness (EDS) in these patients. Additionally, neuropsychiatric symptoms and fatigue, which are also described in SLE, can contribute to sleep changes and secondary EDS[6]. Depressive mood and anxiety interfere with daily coping adding to further disabilities in these individuals[7]. Sleeping problems and depressive symptoms have been reported as being one of the under recognized needs of SLE patients[8].

Pulse intravenous (i.v.) cyclophosphamide may be beneficial to patients with severe forms of nephritis and central nervous system complications[9,10]. Intravenous pulse therapy with cyclophosphamide may provide a less toxic alternative to oral therapy and can be more cost-effective[11,12]. Despite the various reports on the adverse effects secondary to cyclophosphamide, there is a lack of information regarding the occurrence of depressive symptoms and sleep disorders.

The aim of this study was to evaluate the presence of sleep disturbances and depressive symptoms in critically ill SLE patients receiving i.v. cyclophosphamide.

METHODS

Subjects

Thirty-five consecutive SLE patients receiving i.v. cyclophosphamide were eligible to take part into the study. Exclusion criteria were recent severe infectious disease, end-stage renal disease, recent convulsions, paralysis, upper motor neuron signs, or other localizing sign indicating brain involvement, or unwillingness to participate into the study. Five were excluded due to recent infectious illness (n = 2) or unwillingness to participate (n = 3). None of the subjects were on use of sedatives, antidepressives or neuroleptics. Thirty consecutive patients of either gender aged 14 to 53 years with clinical and laboratory diagnosis of SLE according to American College of Rheumatology were finally recruited[13]. Financial compensation was not provided for any subject. The study protocol was approved by the local Ethics Research Committee and written informed consent was obtained in all cases.

Study design

This was a cross-sectional study of consecutive patients undergoing i.v. pulse therapy with cyclophosphamide. This is a standardized procedure performed at outpatient clinics. The standardized CP scheme, provided as an out-patient service at HUWC, consist of: induction period – venous infusions of cyclophosphamide during six months; maintenance period – bymonthly infusions during six months, then quarterly infusions until completing 24 months. The initial dose is 750 mg/m² (500 mg/m² if creatinine clearance is less than one third of normal), then 1 g/m² with dose adjustments in accordance with leucocyte and platelet levels. If the leucocyte count is below 1.500/mm³ on the 14th day post-pulse, the following dose will be reduced by 25%. If the disease remains active after the first six months of treatment the induction period scheme may be repeated up to three times. On the day scheduled for CPT patients should be in possession of urine and complete blood tests performed within the last 24 hours. If no contraindication is given by the rheumatologist during clinical examination, the medication is prescribed and administered on the same day along with 2-3 liters of endovenous glucose saline solution to boost diuresis, as well as antiemetics (8 mg ondansetron endovenously) immediately before and 3 hours after the procedure, or at doctor's discretion. Usually, patients are receiving concomitant steroids, with variable dosages. All patients studied were considered clinically stable, with no signs of infectious, trauma or acute complications in the 3 months prior to the study, as assessed by their clinical history and a review of their medical records. Two previous trained clinical assistants applied a questionnaire for sociodemographic and clinical data while patients were receiving the medication. Demographics and clinical data were recorded using a closed-question data collection instrument. Immunological and biochemical test results were collected from medical records. Comorbidities were determined by interview and file review. Body mass index (BMI) was calculated as the ratio between weight (kg) and squared height (m). All variables were measured concurrently.

Assessment procedures

Sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI)[14]. This scale has seven components, each one dealing with a major aspect of sleep: 1) subjective quality of sleep; 2) sleep onset latency; 3) sleep duration; 4) sleep efficiency; 5) presence of sleep disturbances; 6) use of hypnotic-sedative medication; and 7) presence of daytime disturbances, as an indication of daytime alertness. Individuals with total PSQI score of six or more were considered poor sleepers. Daytime somnolence was assessed using the Epworth Sleepiness Scale. The Epworth Sleepiness Scale is a validated questionnaire containing eight items that ask for expectation of dozing in eight hypothetical situations. Dozing probability ratings range from zero (no probability) to three (high probability). An Epworth Sleepiness Scale score of 10 or more indicates EDS[15]. Symptoms of depression were evaluated using the 21-item Beck Depression Inventory (BDI)[16]. A cut-off of 19 defined the presence of depression. All patients had a clinical and neurological examination. SLE clinical activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[17].

Statistical analysis

All data are presented as mean ± SEM. For statistical analysis and data description patients were stratified as normal or poor sleepers and according to the presence of EDS. Logistic regression analysis was used to test for factors associated with poor quality sleep and EDS. Significance level was accepted at 95% ($p < 0.05$). All data were analyzed using a Statistic Package for Social Sciences (SPSS- Norusis, 1993) software for Windows.

RESULTS

Subject characteristics are given in table 1. The disease first appeared at a mean age of 25.4 ± 10.2 (range 8 - 51 years). Most patients were female. A BMI > 25 was present in 7 subjects (23.3%). Common comorbidities were systemic arterial hypertension (30%), anemia (23.3%), osteoporosis (23.3%), cardiopathy (6.6%) and seizures (3.3%). Most common medications on use were prednisone (N = 27, 90.0%; dose from 10 - 20 mg/day), cloroquine (N = 7, 23.3% dose from 150 mg - 250mg/day), captopril (N = 10, 33.3%; dose from 12.5 to 75.0 mg/day), hydrochlorothiazide (40.0%, 25 mg/day), calcium carbonate (N = 12, 40.0%, 2000 mg/day) and ferrous sulfate (N = 6, 20.0%; 300 mg/day). One patient was using carbamazepine (600 mg/day) to prevent seizure. Previous history of headache was detected in 12 subjects (40.0%) and psychosis in five (16.6%). Common indications for initiation of i.v. cyclophosphamide therapy included the presence of lupus nephritis (56.6%), cytopenia (26.6%) and neurologic manifestations (16.6%).

Table 1
Demographic and clinical characteristics of study subjects

Number of subjects	30
Age, y (Mean ± SD)	30.5 ± 10.0
Female, n (%)	27 (90%)
Age at diagnosis (y) (Mean ± SD)	25.4 ± 10.2
Disease duration (Mean ± SD)	5.1 ± 4.4
BMI (Mean ± SD)	24.2 ± 4.3
Dose of cyclophosphamide at time of evaluation (Mean ± SD)	948.27 ± 221.39
SLEDAI > 5, n (%) (Mean ± SD)	23 (76.6) 17 ± 11.4
Excessive daytime sleepiness (ESS >10), n (%) ESS scores (Mean ± SD)	9 (30%) 8.5 ± 4.9
Poor quality sleep (PSQI > 6), n (%) PSQI scores (Mean ± SD)	20 (66.6) 7.8 ± 3.9

PSQI = Pittsburgh Sleep Quality Index; BMI = Body Mass Index; y = years; m = months; SLEDAI = Systemic Lupus Erythematosus disease activity index; ESS = Epworth Sleepiness Scale.

Mean global PSQI score was 7.8 ± 3.9 and poor quality sleep (PSQI ≥ 6) was diagnosed in 20 patients (66.7%). SLEDAI evaluation, ranging from 2 to 46 (17 ± 11.4), was related to global scores of the PSQI (ANOVA, F = 5.9, p = 0.02). Excessive daytime sleepiness, as assessed by the Epworth Sleepiness Scale (8.5 ± 4.9), was present in 9 cases (30%). Excessive daytime sleepiness was not related to any of the studied measures. Twelve patients (40%) were considered depressed (BDI > 19). Poor sleep quality was associated with the presence of symptoms of depression assessed by the BDI (p = 0.03) (Table 2). In this study, SLEDAI activity was not related to the presence of depressive symptoms (p = 0.15). Sleep disturbance and depressive symptoms are similar to other reported series in the literature (Table 3).

DISCUSSION

This study describes the occurrence of sleep disturbances and depressive symptoms in critically ill SLE patients on i.v. cyclophosphamide. It is interesting to know that our data are similar to other studies reported in the literature.

Table 2
Logistic regression analysis between poor quality sleep (PSQI score ≥ 6) and clinical and laboratory parameters

Parameters n	PSQI < 6 (n = 10)	PSQI ≥ 6 (n = 20)	Odds ratio (95% CI)	P value
Age, y	29.3 ± 9.3	33.3 ± 11.7	0.99 [0.91–1.07]	0.82
Disease duration (y)	4.2 ± 3.1	5.5 ± 5.0	1.00 [0.99-1.02]	0.39
Age at diagnosis (y)	24.4 ± 9.1	27.7 ± 12.7	0.97 [0.90–1.05]	0.58
BMI (kg/m²)	24.5 ± 4.5	23.8 ± 4.2	0.96[0.79–1.17]	0.73
SLEDAI	12.9 ± 8.5	26.4 ± 12.3	1.03 [0.96–1.11]	0.37
ESS score	7.2 ± 2.9	11.5 ± 7.2	1.06 [0.90–1.26]	0.46
Depression (present/absent)	6/4	6/14		
(% values)	60/40	30/70	0.09 [0.01–0.85]	0.03*

PSQI = Pittsburgh Sleep Quality Index; BMI = Body Mass Index; y = years; SLEDAI = Systemic Lupus Erythematosus disease activity index; ESS = Epworth Sleepiness Scale.

Table 3
Summary of previous related studies on sleep disturbances and anxiety-depression symptoms in systemic lupus erythematosus

	SLEEP DISTURBANCE	ANXIETY-DEPRESSION
Costa *et al.* 2005 (Ref. 19)	56%	
Moses *et al.* 2005 (Ref. 8)	70%	Depression 69%
Valencia-Flores *et al.* 1999 (Ref. 5)		Mild depression 38%
Sanna *et al.* 2003 (Ref. 21)		Mood disorders 16.7% Anxiety 3.7%
Iverson *et al.* 2002 (Ref. 18)	70.7%	Possibly depressed 46% Probably depressed 39%
Brey *et al.* 2002 (Ref. 20)		Anxiety 27.2% Major depressive-like episode 37.2%
Ainiala *et al.* 2005 (Ref. 2)		Mood disorder 43%
Tench *et al.* 2000 (Ref. 26)	60%	

Our results show that poor quality sleep is highly frequent similar to previously reported series of SLE cases on other form of therapy[8,18,19]. Also, it is related to disease activity and to the presence of depressive symptoms[8,18]. Poor quality sleep in association with depressive symptoms has been previously described in less affected patients[19]. The variable frequency of depressive symptoms described in SLE patients may be due to the different methods of evaluation and to different degrees of illness severity[20,21].

In this study, disease activity was related to the global score of the PSQI supporting the hypothesis that intrinsic disease factors generate sleep problems in SLE. There is evidence for a reciprocal role of the immune system in sleep. Sleep disturbances are believed to be both a cause and a consequence of various immune and autoimmune conditions[22]. Immune mediators have been connected to sleep changes in other clinical[23,24] and experimental conditions[25]. Previously, it has been hypothesized that sickness-motivated behavior influence neuropsychiatric manifestations including sleep patterns[26]. On the other hand, experimental evidence indicates that sleep deprivation provokes early manifestation of the disease and corticosteroid secretion[27]. Fatigue, a common complaint of patients with SLE, has been linked to reduced daytime performance[28]. It should be kept in mind that EDS can be mistaken for fatigue. Vague symptoms of physical fatigue may lead to semantic confusion and a proper investigation into the occurrence of EDS and poor quality sleep may be overlooked. EDS has a negative impact on performance and is associated with impaired concentration, memory and mood disturbances. The Epworth sleepiness scale is an important clinical tool to identify subjective daytime sleepiness and is largely used in sleep disturbance screening. Therefore, it is worthwhile to identify poor quality sleep and EDS in order to improve quality of life in SLE. EDS may be secondary to multiple causes and this can be a challenge to the therapeutic management of SLE. To our knowledge, therapeutic benefit with sleep hygiene and pharmacological therapy has not yet been systematically attempted in these patients.

Intravenous pulse therapy with cyclophosphamide may provide more cost-effectiveness, long-term benefits. Although it is believed to be a less toxic alternative to oral therapy, long prospective comparative trials are still needed to establish toxicity and risk profile[29].

In summary, sleeping problems and depressive symptoms are frequent and yet an under recognized and unmet need in SLE patients, regardless of the specific therapy. We suggest that therapy for depressive symptoms might be instrumental for the management of fatigue, sleep disturbance and disease activity.

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