A two-phase cohort study of the sleep phenotype within primary Sjögren's syndrome and its clinical correlates

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ABSTRACT

Objective. *To characterise the sleep profile of patients with primary Sjögren's syndrome (pSS) and its relationship between hyper-somnolence and other clinical parameters.*

Methods. *In phase one of the study, we utilised cross-sectional data on daytime hyper-somnolence from the United Kingdom Primary Sjögren's Syndrome Registry (UKPSSR) cohort (n=857, female=92.7%). Phase two relied on clinical data from a cohort of patients (n=30) with PSS, utilising symptom assessment questionnaires and sleep diaries.*

Results. *Within the UKPSSR, daytime hyper-somnolence was prevalent (ESS, 8.2±5.1) amongst pSS patients with a positive correlation between daytime hyper-somnolence and fatigue (Spearman's r_s=0.42, p<0.0001). Amongst the clinical cohort, 100% of patients had problematic sleep. Participants with pSS awoke frequently (NWAK, 2.2±1.3), had difficulty in returning back to sleep (WASO, 59.9±50.2 min vs. normal of <30min) and a reduced sleep efficiency (SE, 65.7±18.5% vs. >85%). Fatigue (FIS, 82.4 ±33.5) and orthostatic symptoms (OGS, 6.7±3.7) remained high in these patients.*

Conclusion. *Sleep disturbances are a problem in pSS, comprising difficulty in maintaining sleep, frequent awakenings throughout the night and difficulties in returning back to sleep. As such, the total time in bed without sleep is much greater and sleep efficiency greatly reduced. These patients in addition have a high symptomatic burden possibly contributing to and/or contributed by poor and disordered sleep.*

Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterised by sicca symptoms (1, 2) and extraglandular manifestations, including fatigue (3), orthostatic intolerance (4), pain (5) and depression (6). It remains one of the most prevalent autoimmune diseases, with a reported prevalence between 0.1% and 4.8% in various populations (7). It may occur at any age, yet affects mainly females in the fifth decade of life, with a female-male ratio typically 9:1 (7)

Severe fatigue is a common feature of pSS, reported in up to 75% of patients (8) and is strongly correlated with poor quality of life (9-11).

Sleep disturbances have previously been reported in pSS patients (12, 13) with a recent systematic review identifying an increased prevalence of subjective and objective sleep disturbances, including hyper-somnolence in these patients compared with controls (14).

Despite these reports, little is known about the relationship between hyper-somnolence and other clinical parameters.

There are two objectives to this study. Firstly, we report on the symptom of hyper-somnolence in a well-defined cohort of pSS patients. Secondly, we examine patient-reported sleep diary data from a cohort of pSS patients presenting to a multidisciplinary fatigue clinic.

Methods

The study was split into two phases. In phase one of the study, we explored the impact of sleep disturbances in pSS through examining cross-sectional data from the United Kingdom Primary Sjögren's Syndrome Registry (UKPSSR) cohort. Phase two of the study involved examining routine clinical data from a cohort of patients with a known diagnosis of pSS presenting to a multi-disciplinary fatigue clinic.

Phase one:
United Kingdom Primary Sjögren's Syndrome Registry

The data were given with permission

from the UKPSSR in order to explore daytime hyper-somnolence in patients with pSS. The UKPSSR is a national cohort of pSS patients diagnosed according to the American European Consensus Group (AECG) criteria and biobank and includes a range of clinical data and samples which are captured at the time of recruitment using a standardised proforma as described previously (15). All participants provided informed consent according to the principles of the Helsinki Declaration. Research ethics approval was granted by the North West Research Ethics Committee in the UK.

Phase two

Participants

A total of 269 consecutive patients attended the CRESTA Fatigue clinic (Newcastle upon Tyne, UK) between March 2013 and February 2016 and routinely complete symptom questionnaires and sleep diaries as part of their multidisciplinary assessment. A total of 30, patients who had been diagnosed with pSS by a physician according to the AECG criteria, presented to the clinic for assessment during this time and brought the completed symptom questionnaires to their first appointment. The symptom assessment questionnaires have been used in previous studies. Patients were not taking concurrent hypnotics or benzodiazepines.

Outcome measures

The following symptom assessment tools were used to evaluate all participants. Symptom assessment questionnaire return rate was 80% (144/180).

• *Fatigue impact scale (FIS)*

The FIS (16) is a 40-item generic scale of fatigue impact which is used to assess fatigue severity. This scale has previously been validated and extensively used in chronic fatigue syndrome patients. Possible scores range from 0-160 with higher scores representing increased fatigue.

• *Cognitive failures questionnaire (CFQ)*

The CFQ measures self-reported failures in perception, memory and motor function (17). The questionnaire consists of 25 items, each graded on a scale of 0–4; adding the scores for the individual items creates a total score.

• *Hospital anxiety and depression scale (HADS)*

The HADS (18) is a 14-item measure of current anxiety (HADS-A) and depression (HADS-D). Caseness for anxiety or depression is revealed by subscores greater than 11. With borderline anxiety and depression revealed by subscores 8–10 inclusive.

• *Epworth sleepiness scale (ESS)*

In view of the association between excessive daytime sleepiness and fatigue, all subjects completed the ESS questionnaire (possible score range 0-24) (19). This fully validated tool assesses daytime hypersomnolence, with a score ≥10 being indicative of significant hypersomnolence during the day.

• *Orthostatic grading scale (OGS)*

Subjects completed the OGS, a fully validated self-reported tool to assess the symptoms of orthostatic intolerance due to orthostatic hypotension (*e.g.* severity, frequency and interference with daily activities) (20). The OGS consists of five items, each graded on a scale of 0–4; adding the scores for the individual items creates a total score of 0–20.

Sleep diaries

Participants were required to complete standard 14-day sleep questionnaires. They recorded time they awoke (WAKE), rose from bed (RISE), went to bed (BED), turned lights of (LIGHTSOUT), sleep onset latency (SOL), number of nightime awakenings (NWAK), amount of time awake after the onset of sleep (WASO), and perceived total sleep time (self-reported, or s/r TST). The following sleep variables were calculated: total sleep time (TST), time in bed (TIB), time in bed without sleep (TIB w/o sleep) and sleep efficiency (SE%). 100% returned their sleep diaries. Normal sleep diagnostic values were used (21) wherein SOL ≤30 minutes, WASO ≤30 minutes, TST ≥360 minutes, s/r TST ≥360 minutes and SE ≥85%.

Table I. Cohort characteristics in participants with primary Sjögren's syndrome (PSS).

	pSS
n.	857
Female	795 (92.7%)
Age	58.1 (±12.7)
ESS	8.2 (±5.1)

Data from the United Kingdom Primary Sjögren's Syndrome Registry (UKPSSR) Data. ESS: Epworth sleepiness scale. Values are given as mean ± SD unless otherwise stated.

Sleep quality

Participants were required to rate, on a scale of 0–4, their morning wellbeing and enjoyment of the sleep, in addition to how mentally alert and physically alert they perceived themselves to be following that night's sleep.

Statistical analysis

All statistical analyses were performed using GraphPad Prism v. 7.00 (Windows, GraphPad Software, San Diego, CA, USA). All data were normally distributed. Comparisons were therefore made between proportions in each group using Fisher's exact test and between continuous variables using the independent two-tailed Student's *t*-test. The level of significance was set at $p<0.05$. All values are expressed as mean ± SD unless otherwise stated.

Results

Phase one:

United Kingdom Primary Sjögren's Syndrome Registry

We sought to explore daytime hypersomnolence in pSS patients and identify correlates of sleep disturbance. As such we examined data on daytime hypersomnolence from the UKPSSR (Table I). A total of 857 participants were identified from the UKPSSR with pSS. This comprised of 92.7% (795/857) females with a mean age of 58.1±12.7 years. There was a prevalence of daytime hypersomnolence (ESS, 8.2±5.1) amongst the pSS patients, with a positive correlation between daytime hypersomnolence and fatigue (Spearman's $r_s = 0.42$, $p<0.0001$) (Table II).

Phase two:

CRESTA fatigue clinical data

To explore sleep disturbances further,

Table II. Correlation between Epworth Sleepiness Scale (ESS) and other variables. The data are from the United Kingdom Primary Sjögren's Syndrome Registry (UKPSSR).

ESS vs.	Mean	SD	r	*p*-value
ESS	8.19	5.1	-	-
Age (yrs)	58.1	12.69	-0.137	0.00006
Female			-0.002	0.94
Symptom duration (yrs)	11.66	9.86	0.018	0.59
Age symptoms started (yrs)	46.36	14.2	-0.122	0.0003
Age diagnosed (yrs)	52.27	13.07	-0.120	0.0004
Anti-Ro present	-	-	0.015	0.65
Anti-La present	-	-	0.009	0.79
Disease activity index score (ESSDAI)	4.9	4.92	0.069	0.04
Disease activity index score without biological domain (ClinESSDAI)	5.05	5.54	0.086	0.012
Health status (EQ5D-TTO)	0.63	0.3	-0.296	<0.0000001
EULAR-SS	5.87	2.52	0.220	<0.0000001
Overall ESSPRI score	5.37	2.19	0.379	<0.0000001
Fatigue	5.56	2.65	0.420	<0.0000001
Dryness	6.01	2.53	0.200	<0.0000001
Pain	4.55	2.96	0.301	<0.0000001
Mental fatigue	3.97	2.74	0.427	<0.0000001
Ocular dryness	5.59	2.77	0.231	<0.0000001
Oral dryness	6.01	2.81	0.177	<0.0000001
Skin dryness	3.89	2.84	0.296	<0.0000001
Nasal dryness	3.58	2.92	0.278	<0.0000001
Tracheal dryness	3.59	3.01	0.310	<0.0000001
Vaginal dryness	4.39	3.98	0.116	<0.0000001

ClinESSDAI: Clinical European League Against Rheumatism (EULAR) Sjögren's syndrome (SS) Disease Activity Index (DAI); ESSDAI: European League Against Rheumatism (EULAR) SS Disease Activity Index (DAI); ESSPRI: European League Against Rheumatism (EULAR) SS Patient Reported Index; EQ5D-TTO: EuroQol 5 Domain-Time Trade Off Method; EULAR-SS: European League Against Rheumatism (EULAR) SS.
Values are given as mean ± SD unless stated otherwise. Correlation calculated using Pearson Correlation. *p*-values given with $p<0.05$ considered statistically significant.

Table III. Sleep diaries in participants with primary Sjögren's syndrome (pSS) as compared to normal sleep as characterised previously (18).

	pSS	Normal sleep (18)
n.	30	
Females (%)	30 (100%)	
Age (years)	62.6 (±13.5)	
SOL (min)	26.4 (±30.4)	<30min
NWAK (times)	2.2 (±1.3)	
WASO (min)	59.9 (±50.2)	<30min
s/r TST (min)	358.0 (±117.9)	
TST (min)	366.2 (±117.8)	>360min
TIB (min)	554.7 (±72.4)	
TIB without sleep (min)	188.5 (±105.5)	
SE %	65.7 (±18.5)	>85%
Quality average	2.01 (±0.4)	

NWAK: number of awakenings; SE: sleep efficiency; SOL: sleep onset latency; TIB: time in bed; s/r TST: self-reported total sleep time; TST: total sleep time; WASO: amount of time awake after the onset of sleep. Values are given as mean ± SD unless otherwise stated.

we examined sleep diary data from a cohort of pSS patients presenting to a fatigue clinic and explore self-reported sleep disturbances. A total of 30 participants were identified as having pSS. This comprised 100% (30/30) females with a mean age of 62.6 (±13.5) years. There was a 100% (30/30) sleep diary return rate. Taking into account that each participant is asked to complete 6-symptom assessment questionnaire at the time of assessment, there was a corresponding return rate of 80% (144/180).

Normal and problematic sleep diaries

We classified normal sleep (20 as average SOL and WASO of not exceeding 30 minutes, TST of greater than 360 minutes and SE% greater than 85%. Based on this, 100% (30/30) of participants with pSS have problematic sleep, as can be seen in Table III.

Time between turning the lights off and the first episode of stage 2 sleep was typically normal in pSS (SOL, 26.4±30.4 min) as compared to normal sleep of <30 minutes. Participants with PSS awoke frequently (NWAK, 2.2±1.3), and the amount of time spent awake after the first episode of stage 2 sleep was significantly longer in pSS participants as compared to normal sleep (WASO, 59.9±50.2 min *vs*. <30min).

Total sleep time was slightly longer than normal sleep (TST, 366.2±117.8 min *vs*. >360 min), however sleep efficiency was much reduced in those with pSS (SE, 65.7±18.5% *vs*. >85%), suggesting participants are spending considerable amounts of time in bed and not sleeping (TIB w/o Sleep, 188.5±105.5min). As such quality of sleep was poor in those with pSS (2.01±0.4).

Symptom assessment questionnaires

In order to ascertain the symptomatic burden on these participants, we undertook a series of symptom assessment questionnaires (Table IV). Caseness for anxiety and borderline for depression met in participants with pSS. In addition fatigue and orthostatic symptoms remained high in these same participants.

Discussion

We present some novel findings in this paper. Firstly, daytime hypersomnolence is prevalent in pSS and correlates with fatigue, with data from a national research biobank. Secondly in a cohort of 30 pSS patients presenting to a fatigue clinic, difficulty in maintaining sleep rather than initiating sleep occurs. Thirdly, pSS patients spend significant periods of time in bed without sleep resulting in reduced sleep efficiency. Fourthly, pSS patients as such have overall poor quality of sleep. Finally, pSS patients have a high symptomatic burden comprising high levels of fatigue, orthostatic symptoms, and increased rates of anxiety, depression and deficits in perception, memory and motor function.

Table IV. Symptom assessment questionnaires in participants with primary Sjögren's syndrome (pSS).

	pSS
FIS	82.4 (±33.5)
OGS	6.7 (±3.7)
ESS	8.1 (±5.2)
CFQ	51.9 (±23.5)
HADS A	11.5 (±4.9)
HADS D	8.2 (±4.3)

CFQ: Cognitive Failures Questionnaire; ESS: Epworth Sleepiness Scale; FIS: Fatigue Impact Scale; HADS: Hospital Anxiety and Depression Scale, A: anxiety, D: depression; OGS: Orthostatic Grading Scale. Values are given as mean ± SD unless otherwise stated.

We sought to explore daytime hypersomnolence in patients from a national research biobank (UKPSSR) and identify correlates of sleep disturbances. We found a high prevalence of daytime hypersomnolence amongst patients with pSS. This appeared to correlate with high levels of fatigue in these patients. In order to explore the symptomatic burden of this we examined sleep diary data from a clinic cohort.

Difficulty in maintaining sleep was pronounced throughout the cohort of pSS participants, with difficulty initiating sleep less so. pSS patients have previously been shown to self-report a subjective problem to somewhat initiate and largely maintain sleep (22). This study described these findings using a self-reported sleep questionnaire rating sleep problems from 'no problems' to 'very great problems'. Whereas our study builds upon this through semi-quantitative sleep diaries and a number of symptomatic burden questionnaires. Whilst pSS participants awoke repeatedly throughout the night, we note the total sleep time was only slightly longer than what is characterised as normal sleep (21). With difficulty maintaining sleep this suggests repetitive awakenings with prolonged duration until sleep resumes, resulting in a greater duration of time in bed without sleep and consequently much reduced sleep efficiency. Reduced quality of sleep in pSS participants suggests that non restorative sleep is a feature in this patient group.

Fatigue is a common occurrence in pSS (8) and our findings support this. Previous studies examining fatigue in rheumatic diseases have found that disease activity, especially arthralgia, sleep disturbance, depression and increased physical effort most strongly contribute to fatigue (22). While the exact cause of fatigue in pSS remains unclear, it is most likely that fatigue in pSS is multi-factorial with sleep being one such factor.

Concurrent medication use may affect the sleep phenotype of patients with pSS. In particular patients use of hypnotics or benzodiazepines may affect the sleep phenotype of such patients. Patients in this study were not utilising concurrent hypnotics or benzodiazepines.

We note the presence of increased orthostatic symptoms and intolerance amongst pSS patients. This builds upon previous findings of greater autonomic dysfunction amongst these patients (23-25). Autonomic dysfunction has been proposed as a factor influencing fatigue in pSS patients, and indeed greater autonomic dysfunction correlates with increased fatigue in pSS patients (24).

Impaired sleep in patients with pSS has been shown to confer a significantly higher risk of subclinical atherosclerosis and cardiovascular disease (26). In addition, pSS patients with impaired sleep had greater levels of triglycerides in their serum, further contributing to cardiovascular risk (26). As we show such patients often have an impaired sleep phenotype, we further highlight the need for clinicians to assess and manage sleep in pSS patients.

Sleep disturbances have been noted in other rheumatic diseases. Difficulty in both, initiating and maintaining sleep has been demonstrated in rheumatoid arthritis (26), in addition to diminished self-reported sleep quality (28) with pain proposed as a possible factor. Similarly, within knee osteoarthritis, up to 31% report significant disturbances in initiating sleep and 81% difficulties mainitaing sleep (29).

Pulmonary manifestations of pSS may affect sleep directly or indirectly. Using polysomnography, one study (14) noted the presence of obstructive sleep apnoeas were twice in their pSS group and controls and continuous positive airway pressure (CPAP) treatment was provided. Of the 5 participants with severe sleep apnoea who used CPAP treatment, significant improvements in daytime hypersomnolence were noted. Further research in to this area could offer clinical benefits to these patients.

This study has some limitations. Due to the small sample size of the pSS group (n=30), these findings would need to be repeated in large multi-centred studies. In addition we used a number of questionnaires, and as such their accurate completion is affected by the motivation of the patient. However, the questionnaires were short and have been used in numerous previous studies. In addition, in our experience, fatigued patients tend to be more cooperative and willing to help in research studies than patients with other illnesses, partly due to the widespread negative impression of fatigue in illness. However, this may in turn introduce a degree of selection bias. This reinforces the need to reproduce our findings at other centres. Furthermore our data is from a Fatigue Clinic and therefore may not be representative of the general pSS population, this too reinforces the need to reproduce our findings at other centres.

Sleep disturbances are a problem in pSS, we aimed to explore the phenotype of sleep disturbances in pSS. This is a topic which has been little studied in the past. Utilising a cohort of pSS patients, we have demonstrated a possible sleep profile for these patients. This consists of difficulty maintaining sleep, with frequent awakenings throughout the night and difficulties in returning back to sleep. As such the total time in bed without sleep is much greater and sleep efficiency greatly reduced. These patients in addition have a high symptomatic burden possibly contributing to and/or contributed by poor and disordered sleep.

Key messages

- Severe fatigue is a common feature of pSS.
- A sleep profile exists comprising frequent awakenings and reduced sleep efficiency.
- These patients have a high symptomatic burden contributing to and/or contributed by disordered sleep.

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