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Short Communication

Subjective Sleep Quality as it Relates to Cognitive and Physical Function in Spinal Muscular Atrophy Patients

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Abstract. Sleep quality and its association with cognition has been widely studied in some neurodegenerative diseases, but less is known about this association in spinal muscular atrophy (SMA). In adult SMA ($n = 21$) patients and age-matched controls ($n = 23$), we assessed subjectively measured sleep quality and daytime somnolence. Cognition was assessed with a multi-domain neuropsychological battery. Further, we investigated the association between clinical functional scores and sleep questionnaire scores. Among SMA patients, better motor and limb function was associated with better subjective sleep quality (p's< 0.05). Clinicians should consider sleep quality in patient care and future studies are needed to better understand these relationships.

Keywords: Spinal muscular atrophy, neuromuscular disease, sleep quality, cognition

INTRODUCTION

5q-spinal muscular atrophy (SMA) is a progressive neurodegenerative disorder that primarily affects motor neurons and is characterized by muscle weakness, leading to functional decline [1]. It is an autosomal recessive disorder caused by deletions or mutations on the survival motor neuron (*SMN1)* gene. Disease severity is highly variable and, based on the clinical features and the age of onset, it has previously been further classified into five main phenotypes [1]. Types II and III account for approximately 50% of SMA patients and these patients typically have normal lifespans. Importantly, with the development of therapeutic drugs, this five-phenotype model is changing, as is the clinical course and care needs for patients [2].

In SMA, sleep, and its relationship with cognitive and physical function, has not been extensively studied. Most evidence comes from pediatric SMA patients, one-third of whom have sleep disruption [3]. Among adults, studies in other motor neuron diseases have shown that sleep disorders are common and patients often report nighttime symptoms including insomnia, fragmented sleep, nightmares, snoring, choking, and restless legs [4]. This can translate into daytime symptoms, including sleepiness, fatigue, and concentration and memory problems. The limited evidence in adult SMA patients suggests an association between cognitive and clinical factors [5, 6] and one study found SMA patients have poorer cognitive test performance compared to controls [6]. In this pilot work, we investigated self-reported sleep quality and physical and cognitive function in SMA patients and age-matched healthy controls.

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MATERIALS AND METHODS

Participants

Twenty-one SMA patients were recruited and tested in-clinic. SMA was diagnosed by attending neurologists in our department based on published clinical criteria [7]; diagnosis was confirmed by molecular analysis and all patients carried a loss of function mutation in *SMN1*. All of the patients were treated with Nusinersen. Patient demographic, clinical, sleep, and cognitive test data were collected during in-clinic examinations under the supervision of the attending neurologist. Twenty-three age-matched controls were recruited from the community through ads at the university. Participants were excluded if they had history of psychiatric or somatic illness, other neurological conditions, major brain injury, alcohol abuse, or major depressive disorder. Participants were screened with the Mini Mental State Exam [8]; a score<24, indicating clinically significant cognitive impairment, was grounds for exclusion, but no screened participants scored below this cut-off. All participants provided written informed consent. All procedures were approved by the Ethical Committee of the Azienda Ospedaliera, Padova.

Sleep questionnaires

Sleep was assessed in patients and controls with two self-report questionnaires, the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS). The PSQI assesses sleep quality and disturbances over the previous one-month period and has been validated in Italian populations [9]. It evaluates seven components of sleep: quality, latency, duration, efficiency, disturbances, use of sleep medication, and daytime dysfunction. A score of 5 or higher indicates excessive sleep disruption. The ESS measures daytime sleepiness and is also validated in Italian populations [10]. The ESS asks participants about their "chances of dozing off" during eight typical daily situations and is scored on a Likert scale. A score of 11 or higher indicates significant daytime somnolence.

SMA Functional Measures

SMA patients were evaluated by the Hammersmith Functional Rating Scale Expanded for SMA (HFMSE), consisting of 33 items and assessing a patient's motor function [11]; the Revised Upper Limb Module (RULM), a 20-item assessment of upper limb function [12]; and the Six Minute Walk Test (6MWT), if able, measuring the distance walked by the patient in six minutes [13]. The number of *SMN2* copy, a known modifier of disease severity, was determined in each patient [14].

Cognitive testing

Patients and controls completed a cognitive test battery, consisting of 11 tests assessing multiple cognitive domains. Patients completed the cognitive testing in-clinic, during their stay for regular treatment. Controls completed the cognitive testing in a quiet room, during study testing. We created z-scores of each of the tests and created cognitive domain scores, as previously described [15]. The memory domain included Rey Auditory Verbal Learning Test immediate and delayed recall [16] and digit span forward [17]. The attention and executive function domain included digit span backward [17], Stroop Color-Word Test [18], Trail Making Test (TMT)-A and B [19], Raven Progressive Matrices [20], and phonetic fluency [21]. The visuospatial domain included the Rey-Osterrieth Complex Figure Test immediate and delayed copy [16].

Statistical analysis

Participant characteristics, sleep questionnaire scores, and cognitive test scores were summarized using Chi-squared (categorical) or *t*-tests (continuous). We then fit linear regression models adjusted for age and education, including an interaction term with dummy variables for diagnosis (controls vs. SMA). The dependent variables were the z-scored cognitive domain scores (attention, memory, visuospatial) and sleep questionnaire score (PSQI, ESS) was specified as the independent variable. We additionally fit age-adjusted linear regression models investigating the association between sleep questionnaire score (dependent variable) and functional ability (independent variable) and cognition (dependent variable) and functional ability (independent variable). All statistical analysis was performed using Stata Version 16.1 (StataCorp, College Station, TX) and RStudio, Version (3.6.1).

RESULTS

SMA patients ($n = 21$) had a mean (standard deviation (SD)) age of 31.6 (10.3), a mean disease duration of 6.9 (6.0) years, 48% were men, and mean scores on the HFMSE and RULM of 37.0 (6.1) and 30.2 (8.0), respectively. Only 11 SMA patients were able to complete the 6MWT and the mean score was 356.3 (106.0) meters. One SMA patient was type 2 and 20 were type 3. Finally, 12 patients had 4 *SMN2* copies, eight patients had three copies, and one had one copy. The patient with one copy also carries a c.859G>C (G287R) substitution in exon 7 of the same gene, producing a full-length functional SMN protein [22]. SMA controls ($n = 23$) had a mean age of 35.8 (12.5), 39% were men, and they had significantly more years of education than SMA patients ($p = 0.016$).

There were no statistically significant differences between SMA and control subjects on any of the sleep measures (Table 1). Higher HFMSE (B = –0.06 95% CI –0.12, –0.005, $p = 0.036$) and RULM (B = –0.23 95% CI –0.37, –0.09, $p = 0.003$) scores, indicating better functioning among SMA patients, were associated with better PSQI scores (Table 2). SMA patients, compared to controls, had lower attention domain scores (–0.20 (0.19) vs (0.08 (0.58), $p = 0.040$) (Table 1). However, there were no associations between sleep questionnaire scores and cognition among SMA patients or controls (results not shown). There were also no associations between RULM or HFMSE scores and cognition among SMA patients (results not shown). In sensitivity analyses, we excluded the single SMA patient with obstructive sleep apnea syndrome (OSAS), because it has been linked to the functional and physical changes in neuromuscular disease [23], but found the associations did not change (results not shown). Further, 10 patients had restrictive respiratory pattern, and we examined the correlation between this and Epworth and PSQI scores, but found no significant correlation; however, this may reflect limited power.

DISCUSSION

This study investigated the association between subjective sleep quality and cognition in SMA patients and age-matched controls, but found no evidence of this association, contrary to findings in

Table 1
Participant characteristics by diagnosis, mean (SD) or N (%)

Variable	SMA patients (N = 21)	Controls (N = 23)	*p*-value
Age, years	31.6 (10.3)	35.8 (12.5)	0.227
Male, n (%)	10 (48)	9 (39)	0.570
Education, years	14.2 (3.2)	16.5 (2.98)	**0.016**
Mini Mental State Exam	29.6 (0.99)	30.6 (2.54)	0.085
Z Attention	–0.20 (0.19)	0.08 (0.58)	**0.040**
Z Memory	0.25 (0.50)	0.22 (0.45)	0.840
Z Visuospatial	0.42 (0.49)	0.32 (0.88)	0.645
Pittsburgh Sleep Quality Index			
Quality	0.90 (0.62)	1.13 (0.69)	0.265
Latency	0.81 (0.81)	1.26 (1.32)	0.185
Duration	0.76 (0.77)	0.83 (0.72)	0.776
Efficiency	0.24 (0.62)	0.48 (0.79)	0.273
Disturbances	1.00 (0.32)	1.61 (1.75)	0.124
Medications	0.43 (0.98)	0.13 (0.63)	0.231
Daytime dysfunction	0.81 (0.51)	0.48 (0.59)	0.055
Global	5.14 (2.90)	5.91 (4.10)	0.480
Pittsburgh Sleep Quality Index, score > 5	6 (29)	11 (48)	0.190
Epworth Sleepiness Scale	3.76 (3.18)	5.57 (3.16)	0.066
Epworth Sleepiness Scale, score > 11	0 (0)	2 (9)	0.167

Table 2
Association between functional clinical scores and sleep questionnaires among SMA patients

SMA	HFMSE ($n = 21$)		RULM ($n = 21$)	
	B (95% CI)	p	B (95% CI)	p
PSQI	–0.06 (–0.12, –0.005)	**0.036**	–0.23 (–0.37, –0.09)	**0.003**
ESS	0.05 (–0.02, 0.12)	0.166	0.10 (–0.09, 0.29)	0.269

All models adjusted for age. PSQI, Pittsburgh Sleep Quality Index. ESS, Epworth Sleepiness Scale. HFMSE, Hammersmith Functional Motor Scale Expanded. RULM, Revised Upper Limb Module.

other neuromuscular disease patient populations [24]. However, better physical function was associated with better subjective sleep quality in SMA patients. Because SMA patients are at higher risk of chronic respiratory distress, due to weakening of respiratory muscles as the disease progresses, the association between functioning and subjective sleep quality may be expected; however, we did not observe a correlation between restrictive respiratory pattern and subjective sleep quality. Other studies have, however, shown that in other forms of progressive neuromuscular disease, chronic respiratory problems are associated with daytime sleepiness and sleep deprivation caused by decreased sleep time and sleep efficiency [23]. This has not been extensively studied among adult SMA patients and future work more closely exploring this potential mechanism is warranted.

This is a pilot study and the evidence is preliminary. The findings should be interpreted considering the study's limitations, including a small sample size, cross-sectional design, and subjective measures of sleep. However, sleep questionnaires have shown good validity and reliability [25] and can be useful in a clinical setting where they are maybe the only accessible or feasible tool to measure sleep. Overall, findings point to disrupted sleep and its association with function in SMA patients, and suggests that more studies, delving deeper into these associations, specifically using objective sleep measures are needed.

Understanding the clinical and practical impact of sleep disruption in SMA patients is critical because it can significantly negatively impact quality of life and prognosis and, conversely, sleep intervention studies have been shown to mitigate cognitive, functional, and behavioral symptoms [26]. It may be that, over time, adult SMA patients experience greater sleep disruption than healthy individuals and longitudinal studies using objective sleep measures in SMA patients, as physical function decreases, are warranted. Our work highlights the importance of monitoring sleep among these patients and providing intervention when mandated.

The updated care guidelines adopted in 2007 have led to substantially better outcomes for patients and the most recent advances in therapeutics that target the SMN protein have completed changed SMA patient care [27]. Since 2007, the updated care guidelines have led to substantially better outcomes for patients and the most recent advances in therapeutics that target the *SMN* protein have completely changed SMA care. This study used the older phenotypic classification system; however, as new therapies modify the SMA disease course, patients will be classified differently and will have different care needs. Although these new therapies will modify the disease phenotypes, they are not cures, so exploring sleep disruption and its potential impacts in SMA patients is important for patients across the lifecourse.

STATEMENTS AND DECLARATIONS

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflict of interest

The authors report no relevant conflicts of interest.

Ethics approval statement

All procedures were approved by the Ethical Committee of the Azienda Ospedaliera, Padova. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Patient consent statement

All participants provided written informed consent.

Permission to reproduce material

N/A.

CLINICAL TRIAL REGISTRATION

N/A.

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