Sleep disorders and neuropsychiatric disorders in a pediatric sample of tuberous sclerosis complex

a questionnaire-based study

Moavero, Romina; Voci, Alessandra; La Briola, Francesca; Matricardi, Sara; Toldo, Irene; Mancardi, Maria Margherita; Negrin, Susanna; Messana, Tullio; Mazzone, Luigi; Valeriani, Massimiliano; Curatolo, Paolo; Bruni, Oliviero

Published in:
Sleep Medicine

DOI (link to publication from Publisher):
10.1016/j.sleep.2021.11.010

Publication date:
2022

Document Version
Publisher's PDF, also known as Version of record

Sleep Medicine 89 (2022) 65–70

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Sleep disorders and neuropsychiatric disorders in a pediatric sample of tuberous sclerosis complex: a questionnaire-based study

Romina Moavero [a, b, *], Alessandra Voci [a], Francesca La Briola [c], Sara Matricardi [d], Irene Toldo [e], Maria Margherita Mancardi [f], Susanna Negrin [g], Tullio Messana [h], Luigi Mazzone [a], Massimiliano Valeriani [b, i], Paolo Curatolo [a], Oliviero Bruni [j]

[a] Child Neurology and Psychiatry Unit, Tor Vergata University of Rome, Via Montepellier 1, 00133, Rome, Italy
[b] Child Neurology Unit, Neuroscience Department, Bambino Gesù Children's Hospital, IRCCS, Piazza S. Onofrio 4, 00165, Rome, Italy
[c] Child Neuropsychiatry Unit – Epilepsy Center, ASST SS. Paolo e Carlo, San Paolo Hospital, Milan, Italy
[d] Child Neurology and Psychiatry Unit, Children's Hospital "G. Salesi", Ospedali Riuniti Ancona, Via Corridoni 11, 60123, Ancona, Italy
[e] Pediatric Neurology and Neurophysiology Unit, Department of Woman's and Child Health, Padua University Hospital, Via N. Giustiniani 3, 35128, Padua, Italy
[f] Unit of Child Neuropsichiatry, Department of Clinical and Surgical Neurosciences and Rehabilitation, IRCCS Gaslini, Via Gerolamo Gaslini 5, 16147, Genova, Italy
[g] Epilepsy and Clinical Neurophysiology Unit, Scientific Institute, IRCCS Eugenio Medea, Conegliano, Treviso, Italy
[h] IRCCS Istituto Delle Scienze Neurologiche, UOC Neuropsichiatria Dell'età Pediatrica, Via Altura 3, 40139, Bologna, Italy
[i] Center for Sensory-Motor Interaction, Aalborg University, Fredrik Bajers Vej 7 D3, Aalborg, D-9220, Denmark
[j] Department of Developmental and Social Psychology, Sapienza University, Rome, Italy

ARTICLE INFO

Article history:
Received 9 November 2021
Received in revised form
22 November 2021
Accepted 24 November 2021
Available online 1 December 2021

Keywords:
Tuberous sclerosis
Sleep
Epilepsy
Neuropsychiatric disorders
Sleep disorders
Autism

ABSTRACT

Objective and background: Sleep disorders (SD) are very common in childhood, especially in certain genetic syndromes. Tuberous Sclerosis Complex (TSC) is a genetic syndromesassociated with a high rate of SD, although these are still under-recognized. The aim of this study was to assess the prevalence of SD in TSC, and to evaluate the relationship between sleep, epilepsy and TSC-associated neuropsychiatric disorders (TAND).

Methods: We administered the Sleep Disturbance Scale for Children (SDSC) and the Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD) to parents of 177 children with TSC referring to different Italian centers. We also collected information on epilepsy and TAND.

Results: SDSC score was positive in 59.3% of patients, being positive in 30.4% of patients without and in 63.6% of those with epilepsy ($p = 0.005$). However, in a multivariate logistic model considering anti-seizure medications and nocturnal seizures, epilepsy ceased to be a significant risk factor for positive SDSC (OR = 2.4; $p = 0.17$). As for TAND, SDSC was positive in 67.9% of patients with and in 32.5% of those without TAND ($p < 0.001$). After adding in a multivariate logistic model active epilepsy, age, and pharmacotherapies, TAND continued to be a significant risk factor for positive SDSC ($p = 0.01$, OR = 1.11).

Conclusions: Our results revealed a high prevalence of SD in children with TSC. Epilepsy didn't increase the risk for SD, while a very strong association was found with TAND. An early detection of SD is of utmost importance in order to plan an individualized treatment, that in some cases might also ameliorate behavior and attention.

1. Introduction

Sleep disorders are a common complaint in childhood, being particularly frequent in children with neuropsychiatric manifestations and in certain genetic syndromes [1]. Disrupted sleep in children with neurodevelopmental disorders and/or genetic syndromes might have deleterious effects on parental stress but also

* Corresponding author. Child Neurology Unit, Neuroscience Department, Bambino Gesù Children's Hospital, IRCCS, Piazza S. Onofrio 4, 00165, Rome, Italy.
E-mail address: romina.moavero@opbg.net (R. Moavero).

https://doi.org/10.1016/j.sleep.2021.11.010

on child learning [2,3]. Indeed, sleep deprivation impairs long-term memory preventing the consolidation of learned tasks and alters the neural mechanisms underlying memory and its physiological roots in brain plasticity [4].

Tuberous Sclerosis Complex (TSC) is one of the monogenic syndromes associated with a high rate of sleep disorders. TSC is an autosomal dominant genetic disease characterized by hamartomas in several organs and tissues [5]. Almost all of affected patients present, at least once during lifecourse, a neurological or neuropsychiatric symptom [6]. TSC associated neuropsychiatric disorders (TAND) encompass a large variety of conditions, including epilepsy, intellectual disability, autism spectrum disorders, and attention deficit hyperactivity disorder [6]. TAND also comprises sleep disorders, that are recognized as significantly impacting the quality of life of patients and their families but are still under-recognized and under-treated. A postal survey of 300 individuals with TSC identified sleep problems in 73% of subjects [7]. A subsequent study on 40 children with TSC revealed that problems with settling and night waking were frequent and associated with epilepsy and general daytime behavioral disturbance [8]. A small sample study using polysomnography objectively documented sleep abnormalities in 9 of 10 TSC patients, including reduced total sleep time and efficiency, increased awakenings, and reduced REM sleep [9]. Another study on a small sample of patients with TSC revealed high rates of night wakings, parasomnia and daytime sleepiness [10]. A recent registry study evaluating TSC related manifestations of more than 2000 subjects, found that sleep disorders are the second most common TAND, with a 43.9% overall prevalence [11], but no detail on the type of sleep disorders nor on the association with epilepsy and/or TAND was available. A questionnaire-based study recently published found a total of 17.4% of patients with TSC presenting a positive score [12]. Finally, a recent meta-analysis study evaluated the prevalence of sleep disorders in different genetic syndromes, and it emerged that in TSC insomnia and excessive daytime sleepiness have such a prevalence that they should be considered as part of a priority assessment [1].

Despite this high comorbidity, the pathophysiology underlying the high prevalence of sleep disorders in TSC remains largely unknown.

TSC is caused by the mutation in one of the two tumor-suppressor genes *TSC1* or *TSC2*, respectively encoding for hamartin and tuberin, forming a heterodimer which has the role of inhibiting the so-called mTOR (mammalian target of rapamycin) complex [13]. mTOR plays a clear and crucial role in the formation of TSC typical hamartomas. However, it has become clear that it is also directly responsible for neurologic and neuropsychiatric symptoms, intervening in epileptogenesis as well as in increasing susceptibility to autism spectrum disorders and intellectual disability [14,15] and can also represent a neurobiological substrate contributing to the increased risk for sleep disorders in patients with TSC [16].

Thus, up to now we do not have so much data assessing the real prevalence of sleep disorders in children with TSC with standardized questionnaires, nor we have complete information on the association between sleep disorders and other TSC related manifestations. However, this is a very important topic, since parents of individuals with rare syndromes often consider sleep as an area for which they would like more information and support [17] and it is important to delineate the prevalence and profile of specific sleep disorders in these groups [1].

The aim of this study was to assess the prevalence of sleep disorders in children with TSC, and to evaluate the relationship between sleep, epilepsy and TAND.

2. Methods

2.1. Subjects recruitment

We identified potential subjects for our study among pediatric patients from the Italian Tuberous Sclerosis Association. The study was approved by the Institutional Review Board of our Hospital.

We included all patients fulfilling the following criteria:

1. A definite diagnosis of TSC;
2. Maximum age of 18 years;

Exclusion criteria included the inability to complete the questionnaires.

2.2. Questionnaire structure and procedures

To investigate the presence of sleep disorders in pediatric patients with TSC, we created an online questionnaire using the "Google Forms" tool provided by Google. We asked parents to fill out the anonymous questionnaire by connecting to an internet link sent by e-mail or diffused through the Italian Tuberous Sclerosis Association web channels.

The questionnaire was structured as follows:

1. A first part with general questions relating to TSC clinical features, including the presence of epilepsy and its characteristics (age at seizure onset, seizure frequency, seizure semiology), the presence of comorbid TAND, as well as ongoing therapies;
2. A section containing questions from the two standardized questionnaires used as a screening test for pediatric sleep disorders, the Sleep Disturbance Scale for Children (SDSC) and the Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD).

2.3. Sleep evaluation

2.3.1. SDSC

The SDSC is one of the most used assessment tools for pediatric sleep. It is a parent-report sleep screening survey developed by Bruni et al. [18], whose application has been extended even in preschoolers [19].

The questionnaire consists of 26 items grouped in 6 subscales relating to the major presenting clinical sleep complaints in pediatric age: difficulty in initiating and maintaining sleep factor (DIMS), sleep breathing disorders (SBD), disorders of arousals/nightmares (DA), sleep/wake transition disorders (SWTD), disorders of excessive somnolence (DOES), and sleep hyperhydrosis (SHY). Each item is rated on a five-point scale, and items questioning about desirable and pathological sleep behaviors are reversed in scoring so that a higher score is indicative of more disrupted sleep.

We divided our population into two groups, patients *with sleep disorders* and *without sleep disorders*, according to the results of the SDSC. We considered as having a sleep disturbance those patients with SDSC total score over the cut-off score of 39 indicated by the authors. Indeed, this was found to be the cut-off score with the best diagnostic confidence with a sensitivity of 0.89 and a specificity of 0.74 [18]. For the subscales we considered T-scores (normal if ≤ 70) as reported on the original paper, therefore pathologic scores were $\geq$17 for DIMS, $\geq$7 for SBD, $\geq$6 for DA, $\geq$14 for SWTD, $\geq$13 for DOES and $\geq$7 for SHY.

2.3.2. ESS-CHAD

The ESS-CHAD has been proposed in 2015 [20] as the adapted version for children and adolescents of the Epworth Sleepiness Scale (ESS), developed as a measure of daytime sleepiness in adults. The ESS-CHAD comprises eight questions in which the patient itself or their caregiver has to rate the child's usual chances of falling asleep while doing different activities. The total score is the sum of the eight items' scores and ranges from 0 to 24, with higher scores representing higher sleepiness. A score above 10 is considered representative of excessive daytime sleepiness and may indicate an underlying sleep disorder [21].

2.4. Statistical analysis

RStudio Version 1.4.1106 for Mac was used to perform all our statistical analysis (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.).

Chi-square test with Yates' correction was used to evaluate differences between patients with and without sleep disorders according to other clinical characteristics (such as presence or absence of epilepsy, neuropsychiatric disorders, antiseizure medications, antipsychotic and antidepressant therapies). Where the sample was too small to allow a valid chi-square test, Fisher's exact test was applied.

Wilcoxon two-sample signed rank test was used to compare total scores of sleep questionnaires (SDSC, ESS – ordinal) to clinical characteristics of patients (epilepsy, TAND, antiseizure medication, ….)

Univariate binary logistic regression models have been developed with Sleep disorders/No Sleep Disorders as outcome variable and epilepsy or TAND as possible predictive variables. Multivariate binary logistic regression models have been then developed to estimate the odds of Sleep Disorders (dependent variable), in relation and after adjusting for possible predictive variables, such as age, sex, epilepsy, or TAND in the child.

P values < 0.05 were considered statistically significant.

3. Results

3.1. Demographics and main clinical features

We collected a total of 184 questionnaires, but 7 have been withdrawn due to duplicate or incomplete answers, therefore the final dataset comprised 177 questionnaires.

The mean age at questionnaires' completion was 9.7 years (range 1–18 years, SD 4.7 years, median 9.25 years).

One-hundred-fifty-four patients (87.0%) presented epilepsy, at least at some point in their lifetime. A total of 137 patients (77.4%) were under ASM (antiseizure medications), with a mean of 2 drugs used (range 1–5). As for seizure frequency, seizures were sporadic in 25 patients (22.7%), monthly in 4 (3.6%), weekly in 6 (5.5%), multiweekly in 16 (14.5%), daily in 19 (17.3%), and multidaily in 40 (3.6%). Finally, 44 patients (28.6%) were seizure free, with 36 of them (81.2%) still on ASM.

At least one TSC-associated neuropsychiatric disorder (TAND) was reported by 134 subjects (75.7%). Intellectual disability appeared to be the most frequently reported problem (n = 94, 53.1%), followed by language disturbances (n = 65, 36.7%) and academic difficulties (n = 54, 30.5%). Autism spectrum disorders and attention deficit-hyperactivity disorder have been reported in 20.9% (n = 37) and 11.9% (n = 21) of patients respectively. Other problems reported included mood disturbances (n = 32, 18.1%), anxiety (n = 18, 10.2%) and obsessive-compulsive disorder (n = 17, 5.1%). TAND were treated with antipsychotic drugs in 6 patients (3.4%), and antidepressants in 1 (0.5%).

An existing SD diagnosis was reported by 29 subjects (16.4%), including insomnia and parasomnias (pavor nocturnus, sleepwalking, confusional awakenings). Specific investigations for SD have been performed only in 4 patients (2.2%). A treatment for SD was ongoing in 22 subjects (12.4% of the whole sample), including melatonin (n = 18), antihystaminics (n = 15), and benzodiazepines (n = 4).

3.2. Sleep questionnaires

3.2.1. Sleep Disturbance Scale for Children (SDSC)

SDSC revealed a positive score in 105 patients (59.3%), with a mean total score of 44.9 (range 27–85, SD 13.8). As for SDSC subscales, scores were positive for DIMS in 39 patients (22.0%), for SBD in 34 (19.2%), for DA in 17 (9.6%), for SWTD in 47 (26.5%), for DOES in 18 (10.2%), and for SHY in 17 (9.6%).

3.2.2. Epworth Sleepiness Scale for children and adolescents (ESS-CHAD)

ESS revealed a positive score, and therefore an excessive daytime sleepiness, in 8 patients (4.5%), with a mean total score of 3.6 (range 0–17, SD 3.1).

3.3. Correlation of sleep questionnaires' results and clinical features

3.3.1. Correlation with epilepsy

SDSC was positive in 7/23 patients without epilepsy (30.4%) and in 98/154 patients with epilepsy (63.6%) ($p = 0.005$, $\chi^2 = 7.8174$). This association was also confirmed by a univariate logistic regression analysis (OR = 4, 95% CI 1.55–10.31; $p = 0.004$). However, after adding in a multivariate logistic model the independent variables ASM, and nocturnal seizures, epilepsy ceased to be a significant risk factor for positive SDSC (adjusted OR = 2.4 (0.69–8.3); $p = 0.17$).

The mean (and median) SDSC scores in patients with and without epilepsy were respectively 45.8 (median 42) and 38.7 (median 34) (ranges: epilepsy 27–85; no epilepsy 27–74), and the Wilcoxon two-sample signed rank test gave a p-value of 0.004 ($W = 1119$).

There was no statistically significant association between a positive score in any of the six SDSC subscales and the presence of epilepsy.

Considering only actual active epilepsy, SDSC was positive in 23/44 (52.3%) seizure free patients and in 75/110 (68.2%) of those with persistence of seizures ($p = 0.09$, $\chi^2 = 2.7844$). However, the mean (and median) SDSC scores in patients with and without active epilepsy respectively 47.17 (median 43, range 27–84) and 42.32 (median 40, range 28–85), and the Wilcoxon two-sample signed rank test gave a p-value of 0.02 ($W = 1834$).

Considering the different SDSC subscales, DIMS was positive in 29.1% of patients with active epilepsy versus 11.4% of those with seizure freedom ($p = 0.03$, $\chi^2 = 4.48$). Correlation with other subscales were not significant.

Considering ASM in patients with a history of epilepsy, a positive SDSC score was obtained in 9/18 (50%) patients without ASM, and in 89/136 (65.4%) of those taking ASM ($p = 0.31$, $\chi^2 = 1.0386$). Searching for correlations with specific pharmacological treatment a statistically significant association was found between a positive SDSC score and benzodiazepines assumption ($p = 0.009$, $\chi^2 = 6.6804$).

As for SDSC subscales there were no significant differences for any of the six areas between patients with a history of epilepsy with or without ASM. Indeed, considering specific treatment,

benzodiazepines assumption was associated with higher rates of positive score in the DIMS (43.2% vs 18.5%, p = 0.004, $\chi^2 = 8.1064$), while carbamazepine was associated with significantly lower rates of positive scores in the DOES subscale (4.8% vs. 17.6%, p = 0.04, $\chi^2 = 4.1107$).

ESS positive scores have been detected in none of the 23 patients without a history of epilepsy and in 8/154 patients with a history of epilepsy (5.2%) (p = 0.6). Considering persistence or freedom from epileptic seizures, none of the seizure free patients presented a positive ESS, while 8/110 patients (7.3%) with active epilepsy presented a positive score (p = 0.1).

In particular, the median ESS score in patients with and without active seizures were respectively 4 and 3 (ranges: seizure freedom 0–10, seizure persistence 0–17; means: seizure freedom 2.95, seizure persistence 4.26), and the Wilcoxon two-sample signed rank test gave a p-value of 0.02 (W = 1839.5).

There were no significant differences in ESS final result between patients with a history of epilepsy taking or not ASM (p = 1). Searching for correlations with specific pharmacological treatment a statistically significant association was found between a positive ESS-CHAD and valproic acid (p = 0.01, 95% CI 1.2–85.44, OR 7.75), levetiracetam (p = 0.02, 95% CI 1.02–53.13, OR 7.8) and benzodiazepines (p = 0.005, 95% CI 1.62–665.51, OR 14.1), while patients taking carbamazepine presented lower rates of positive ESS-CHAD scores (9.5% vs 0, p = 0.01, 95% CI 0–0.79, OR 0).

3.3.2. Correlation with TAND

SDSC was positive in 91/134 patients (67.9%) with the presence of TAND and in 14/43 of patients (32.5%) not reporting any neuropsychiatric condition (p < 0.001, $\chi^2 = 15.427$). A univariate logistic regression analysis confirmed that a comorbid neuropsychiatric condition increased the risk of having a positive SDSC score (p < 0.001, OR = 1.48). After adding in a multivariate logistic model the independent variables of active epilepsy, age, pharmacological treatments, TAND continued to be a significant risk factor for positive SDSC (p = 0.01, OR = 1.11). Analyzing the different SDSC subscales, DIMS and SBD positive scores appeared to be significantly associated with TAND. Results are detailed in Table 1.

The median SDSC score in patients with and without a TAND complain were respectively 43 and 35 (ranges: TAND 27–85; no TAND 28–68; means: TAND 47.0; no TAND 38.1) (p < 0.001, W = 1674) (Fig. 1).

Regarding specific neuropsychiatric conditions, the diagnosis that appeared to be significantly associated with a positive SDSC were ASD (p = 0.004, $\chi^2 = 8.0735$), intellectual disability/psychomotor delay (p = 0.003, $\chi^2 = 8.9139$), language disturbances (p = 0.0005, $\chi^2 = 12.06$).

Finally, ESS-CHAD suggested an excessive daytime sleepiness in 8/134 patients (5.9%) with at least one TAND and in none of those without (p = 0.20). The median ESS-CHAD score in patients with and without a TAND complain were 3 in both groups (ranges: TAND 0–17; no TAND 0–9; means TAND:3.8, no TAND:2.9) (p = 0.11, W = 2423.5). Considering specific neuropsychiatric conditions, only anxiety appeared to be statistically significantly associated with a positive ESS-CHAD score (p = 0.004, 95% CI 1.80–64.78).

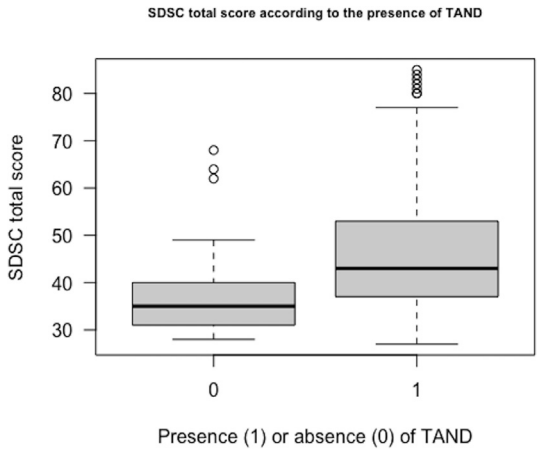

Fig. 1. Chart representing the median SDSC total score in children with (1) and without (0) TAND.

Table 1
Analysis of positive SDSC subscores according to the presence of TAND. Significant p-values in bold.

	TAND (n = 134)	No TAND (n = 43)	*p value*
DIMS	36 (26.9%)	3 (7%)	**0.01**
SBD	32 (23.9%)	2 (4.6%)	**0.01**
DA	16 (11.9%)	1 (2.3%)	0.07
SWTD	38 (28.3%)	9 (20.9%)	0.45
DOES	17 (12.7%)	1 (2.3%)	0.08
SHY	16 (1.9%)	1 (2.3%)	0.07

Abbreviations: TAND Tuberous Sclerosis Associated Neuropsychiatric Disorders; DIMS Difficulties in Initiating and Maintaining Sleep; SBD Sleep Related Breathing Disorders; DA Disorders of Arousal; SWTD Sleep–Wake Transition Disorders; DOES Disorders of Excessive Somnonlence; SHY Sleep related Hyperhydrosis.

4. Discussion

Our study included a wide sample of pediatric patients with TSC, and the results revealed a high prevalence of sleep disorders with a total of 59.3% of patients presenting a pathologic SDSC total score. A couple of previous studies highlighted daytime sleepiness as a significant problem in TSC [1,22], but our results didn't confirm this suggestion, with only 4.5% of patients scoring a positive ESS-CHAD, while the SDSC subscale related to excessive somnolence (DOES) was positive in about 10% of individuals. Indeed, in our sample the disorders of sleep wake transitions appeared to be the most frequently observed (26.5%), followed by difficulties in initiating and maintaining sleep (22%) and disorders of breathing during sleep (19.2%).

The high rate of sleep disorders in patients with TSC is certainly a multifactorial condition, but it now seems evident that there is an underlying neurobiological reason. Indeed, the mTOR pathway has been demonstrated to present strong circadian rhythmicity that correlate with rhythms of protein synthesis [23]. Animal models showed that BMAL1, the core regulator of the circadian clock, is overexpressed in mutated mice, underlying circadian rhythm abnormalities [24]; therefore sleep disorders in TSC, including insomnia, awakenings, or difficulties in falling asleep could be genetically mediated. It has been recently demonstrated that the sleep abnormalities are dependent on the mTOR pathway and a downstream link to increased orexin expression in hypothalamic neurons, thus providing novel insights into the mechanisms of sleep disorders in TSC and suggests innovative, targeted therapeutic strategies involving regulators of mTOR and orexin systems [16]. In this model rapamycin (a selective mTOR inhibitor) and suvorexant (an orexin antagonist) determined an improvement of sleep. However, in clinical literature is still poor on this issue, there is only one study evaluating the effects of everolimus through a questionnaire that investigated even sleep, but without validated questionnaires or standardized measures, and apparently there was no effect [25]. Although our sample of patients was quite wide, the number of children and adolescents taking everolimus in was

too small to address eventual differences in the prevalence of sleep disorders. Of course, this would be of crucial importance since whatever the cause of this comorbidity, sleep disorders are difficult to treat, since patients with TSC and a sleep disorder do not often respond to night-time sedatives or behavioural techniques [26].

Sleep disorders appeared to be significantly related to a personal history of epilepsy but not to the presence of active epilepsy at the time of the interview. However, the significance got lost when considering also antiseizure medication and nocturnal seizures, underlining that these factors could act as confounders. Literature data on the association between sleep disorders and epilepsy in TSC are not concordant [8,10], and we hypothesize that the presence of many factors influencing nocturnal sleep (thus including drugs and seizures interrupting sleep) might influence results of questionnaires. As for the SDSC subscales, none of them resulted to be significantly associated with the presence of a history of epilepsy, and only DIMS appeared to be significantly more frequent in patients with active epilepsy if compared to those with seizure freedom.

Sleep disorders appeared to be significantly more frequent in patients reporting at least one neuropsychiatric disorder, and a statistically significant association was found also for the two subscales of DIMS and SBD. These results confirm that neuropsychiatric disorders confer a high risk for experiencing sleep disturbances, and are in good agreement with a recent paper reporting a positive correlation between SDSC and behavioral/emotional disturbances evaluated with a standardized questionnaire [12].

In the literature there are no significant data reporting a correlation between specific TAND and sleep disorders. Indeed, in our sample, analyzing the different neuropsychiatric conditions, we found a significantly high prevalence of sleep disorders in ASD, intellectual disability/psychomotor delay and even in language disturbances. While it is largely known that ASD and intellectual disability, even in their idiopathic forms, represent risk factors for the presence of sleep disorders [1,27], this association is less known for language disturbances, and although it has been hypothesized that sleep disruption, impacting memory and cognition, can have a deleterious effect on language learning, no definite conclusion is available on this issue [28].

In our study ASD appeared to be significantly associated with a higher rate of positive scores in the subscale of difficulty in initiating and maintaining sleep and also in the one of breathing disorders during sleep. Indeed, ASD in the literature has been associated with a great variety of sleep disturbances, with younger children presenting a greater sleep anxiety, which might determine a difficulty in initiating sleep [27]. Furthermore, it is to note that children with ASD have difficulties in transition between an activity to another, and can perseverate in ritual activities that can make it difficult falling asleep [29,30]. Although some controversial results [31], also the presence of sleep-disordered breathing has been already described as associated with ASD [32], and it was also put in relation with stereotyped activity, social impairment and overall severity of autism symptoms [33]. A significant association with a positive score in the DIMS subscale was also observed in patients with intellectual disability/psychomotor delay.

Our study has some limitations. First, data collection was based on parental reports via questionnaires, therefore some information, both on TSC clinical features and on sleep habits, could be not completely precise. Second, a possible partial influence of a selection bias on our results must be considered: parents of children with more sleep difficulties, and therefore sensitive to the topic, may have answered the questionnaire. Furthermore, although the questionnaire used is able to identify a number of sleep disorders, it can not be sufficient to diagnose specific disturbances such as restless leg syndrome, restless sleep disorders or REM sleep disorders. Future work based on longitudinal analysis of TSC characteristics, TAND and sleep behaviors and alterations, with the use of daily reports or objective sleep measures such as polysomnography or actigraphy, would help to better characterize the relationship between sleep disorders and TSC clinical features.

5. Conclusion

The high prevalence of sleep disorders in the TSC population highlights the need of a specific screening program. This is of utmost importance above all in children with a neuropsychiatric comorbidity, due to the reciprocal interplay between sleep, neurodevelopment and behavior. Since sleep disorders play an active role in exacerbating cognitive and behavioral difficulties, they are a significant focus for clinical intervention.

Although the pathogenesis of sleep disorders in TSC is still largely unknown, the mTOR pathway has been established to play a role, thus opening to possible therapeutic options, although no data are available up to now. Further studies on this issue are desirable in order to understand if this systemic therapy can address such an impacting problem in this population.

Acknowledgements

We are grateful to the Italian Tuberous Sclerosis Association for supporting us in performing this study.

Conflict of interest

The authors declare that they have no conflict of interests.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2021.11.010.

References

[1] Agar G, Brown C, Sutherland D, et al. Sleep disorders in rare genetic syndromes: a meta-analysis of prevalence and profile. Mol Autism 2021;12(1):18.
[2] Chu J, Richdale AL. Sleep quality and psychological wellbeing in mothers of children with developmental disabilities. Res Dev Disabil 2009;30(6):1512–22.
[3] Ashworth A, Hill CM, Karmiloff-Smith A, et al. A cross-syndrome study of the differential effects of sleep on declarative memory consolidation in children with neurodevelopmental disorders. Dev Sci 2017;20(2).
[4] Barone I, Hawks-Mayer H, Lipton JO. Mechanisms of sleep and circadian ontogeny through the lens of neurodevelopmental disorders. Neurobiol Learn Mem 2019;160:160–72.
[5] Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. Lancet 2008;372(9639):657–68.
[6] Curatolo P, Moavero R, de Vries PJ. Neurological and neuropsychiatric aspects of tuberous sclerosis complex. Lancet Neurol 2015;14(7):733–45.
[7] Hunt A. Development, behaviour and seizures in 300 cases of tuberous sclerosis. J Intellect Disabil Res 1993;37(Pt 1):41–51.
[8] Hunt A, Stores G. Sleep disorder and epilepsy in children with tuberous sclerosis: a questionnaire-based study. Dev Med Child Neurol 1994;36(2):108–15.
[9] Bruni O, Cortesi F, Giannotti F, et al. Sleep disorders in tuberous sclerosis: a polysomnographic study. Brain Dev 1995;17(1):52–6.
[10] Trickett J, Heald M, Oliver C, et al. A cross-syndrome cohort comparison of sleep disturbance in children with Smith-Magenis syndrome, Angelman syndrome, autism spectrum disorder and tuberous sclerosis complex. J Neurodev Disord 2018;10(1):9.
[11] de Vries PJ, Belousova E, Benedik MP, et al. TSC-associated neuropsychiatric disorders (TAND): findings from the TOSCA natural history study. Orphanet J Rare Dis 2018;13(1):157.
[12] Zambrelli E, Turner K, Peron A, et al. Sleep and behavior in children and adolescents with tuberous sclerosis complex. Am J Med Genet 2021;185(5):1421–9.
[13] Crino PB. Evolving neurobiology of tuberous sclerosis complex. Acta Neuropathol 2013;125(3):317–32.
[14] Curatolo P, Moavero R, van Scheppingen J, et al. mTOR dysregulation and tuberous sclerosis-related epilepsy. Expert Rev Neurother 2018;18(3):185–201.

[15] Winden KD, Ebrahimi-Fakhari D, Sahin M. Abnormal mTOR activation in autism. Annu Rev Neurosci 2018;41:1–23.
[16] Zhang B, Guo D, Han L, et al. Hypothalamic orexin and mechanistic target of rapamycin activation mediate sleep dysfunction in a mouse model of tuberous sclerosis complex. Neurobiol Dis 2020;134:104615.
[17] Pearson EV, Waite J, Oliver C. Differences in the information needs of parents with a child with a genetic syndrome: a cross-syndrome comparison. J Pol Pract Intellect Disabil 2018;15:94–100.
[18] Bruni O, Ottaviano S, Guidetti V, et al. The Sleep Disturbance Scale for Children (SDSC). Construction and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. J Sleep Res 1996;5(4):251–61.
[19] Romeo DM, Bruni O, Brogna C, et al. Application of the sleep disturbance scale for children (SDSC) in preschool age. Eur J Paediatr Neurol 2013;17(4):374–82.
[20] Johns M. The assessment of sleepiness in children and adolescents. Sleep Biol Rhythm 2015;13(1):97.
[21] Janssen KC, Phillipson S, O'Connor J, et al. Validation of the Epworth sleepiness scale for children and adolescents using rasch analysis. Sleep Med 2017;33:30–5.
[22] van Eeghen AM, Numis AI, Staley BA, et al. Characterizing sleep disorders of adults with tuberous sclerosis complex: a questionnaire-based study and review. Epilepsy Behav 2011;20(1):68–74.
[23] Cao R, Lee B, Cho HY, et al. Photic regulation of the mTOR signaling pathway in the suprachiasmatic circadian clock. Mol Cell Neurosci 2008;38(3):312–24.
[24] Lipton JO, Yuan ED, Boyle LM, et al. The circadian protein BMAL1 regulates translation in response to S6K1-mediated phosphorylation. Cell 2015;161(5):1138–51.
[25] Overwater IE, Rietman AB, Mous SE, et al. A randomized controlled trial with everolimus for IQ and autism in tuberous sclerosis complex. Neurology 2019;93(2):e200–9.
[26] O'Callaghan FJ, Clarke AA, Hancock E, et al. Use of melatonin to treat sleep disorders in tuberous sclerosis. Dev Med Child Neurol 1999;41(2):123–6.
[27] Mazzone L, Postorino V, Siracusano M, et al. The relationship between sleep problems, neurobiological alterations, core symptoms of autism spectrum disorder, and psychiatric comorbidities. J Clin Med 2018;7(5).
[28] McGregor KK, Alper RM. Sleep disorders as a risk to language learning and use. EBP Briefs 2015;10(1):1–21.
[29] Kotagal S, Broomall E. Sleep in children with autism spectrum disorder. Pediatr Neurol 2012;47(4):242–51.
[30] Harvey AG. A cognitive model of insomnia. Behav Res Ther 2002;40(8):869–93.
[31] van der Heijden KB, Stoffelsen RJ, Popma A, et al. Sleep, chronotype, and sleep hygiene in children with attention-deficit/hyperactivity disorder, autism spectrum disorder, and controls. Eur Child Adolesc Psychiatr 2018;27(1):99–111.
[32] Liu X, Hubbard JA, Fabes RA, et al. Sleep disturbances and correlates of children with autism spectrum disorders. Child Psychiatr Hum Dev 2006;37(2):179–91.
[33] Hoffman CD, Sweeney DP, Gilliam JE, et al. Sleep problems and symptomology in children with autism. Focus Autism Other Dev Disabil 2005;20(4):194–200.