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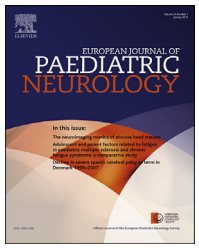

Original article

More daytime sleepiness and worse quality of sleep in patients with Dravet Syndrome compared to other epilepsy patients

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ABSTRACT

Aim: Sleep problems are often reported in patients with a Dravet Syndrome (DS). In this study we explored the sleep behavior in DS and compared the prevalence of sleep problems with other epilepsy patients.

Methods: An online questionnaire based on the '*Sleep Behavior Questionnaire by Simonds & Parraga (SQ-SP)*' was distributed amongst DS parents and a control group (parents from children with epilepsy). Completed questionnaires were evaluated by factor scores and Composite Sleep Index (CSI).

Results: Fifty-six responses were recorded in the DS group (42 were ≤18 year). Caregivers reported an overall frequency of sleep problems in 42.3% (22/52). Severe sleep problems, measured by CSI, were found in 28.3% (13/46) mainly related to night waking or daytime sleepiness. In the control group (n = 66, 62 were ≤18 year), sleep problems were reported by 21.2% (14/52) of the parents. Comparison analysis between pediatric DS and epilepsy patients revealed no significant differences between the prevalence of different types of sleep disorders, except for daytime sleepiness ($p = 0.042$). However, the parent (or caregiver)-reported quality of sleep was significantly lower in the DS group ($p = 0.011$).

Interpretation: Sleep problems are frequent in DS patients and are mainly related to daytime sleepiness and night waking. Compared with other epilepsy patients, severe sleep problems are not more common in patients with a DS. However DS patients tend to have more mild night waking problems, which may explain the worse parental-reported sleep quality in DS patients.

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1. Introduction

Dravet Syndrome (DS) is a genetic epilepsy syndrome with an incidence between 1/15 700 and 1/40 000.[1,2] This syndrome is characterized by refractory seizures, a developmental delay and non-epileptic features.[3–5] In more than 80% a mutation in *SCN1A*, coding for the α1-subunit of voltage gated sodium channels, can be found.[1,3,4] It is recognized that haploinsufficiency of *SCN1A* affects GABAergic neurons in various regions of the central nervous system which explain the different manifestations like seizures, ataxia, crouch gait and sleep problems.[3,6]

Although it is known that people with epilepsy more often have sleep problems,[7,8] the reported prevalence in DS patients seems to surpass this. Concerns about sleep disorders are mentioned by 75 up to 97% of the parents from children with DS.[5,9–11] Nolan et al. conducted a semi-structural interviews with parents from children with DS whereby 22 out of 24 (91.7%) reported sleep problems.[12] Recently, Licheni et al. identified sleep problems in 75% of their DS patients.[10] A review of the polysomnography of 6 DS patients could not identify any specific abnormality in the sleep macro-architecture although the micro-architecture showed an increased cyclic alternating pattern, suggesting a cortical synaptic immaturity.[13]

Animal studies also showed sleep disturbances in DS mice models[14,15] and zebrafish.[16] Kalume et al. could demonstrate that the sleep disorders in his DS mouse model arise from an impaired Na_v current and excitability of GABAergic neurons in the reticular nucleus of the thalamus,[14] suggesting a direct role for *SCN1A* in the regulation of sleep.

Sleep problems have a major negative impact on the quality of life of patients and their caregivers. They can exacerbate behavior problems, disturb the cognitive functioning[17,18] and provoke seizures.[19] Sleep deprivation is a major problem in caregivers of children with severe epilepsy like DS.[20] Many caregivers lack restful sleep due to the fear of life-threatening seizures in their child's sleep or sudden unexplained death in epilepsy (SUDEP) which leads to exhaustion and fatigue.[4,11,21]

In this study we explored the sleep behavior and prevalence of different types of sleep problems in a large cohort of DS patients and compared the results with a control group consisting of children with epilepsy.

2. Method

2.1. Study population, recruitment method and survey distribution

An online Dutch survey was distributed through Qualtrics Survey Software (Qualtrics, Provo, UT, USA) and was announced in a newsletter from the Dutch Dravet League. Patients above the age of 6 months with a clinical diagnosis of a DS could participate. Informed consent had to be given before the start of the questionnaire. Patients were included in the statistical analysis if at least the demographic information as well as the epilepsy features from the online questionnaire were completed. The study was approved by the ethics committee of the Antwerp University Hospital.

2.2. Sleep questionnaire

The survey consisted of the Dutch translation of the '*Sleep Behavior Questionnaire by J.F. Simonds & H. Parraga (SQ-SP), modified version for use in individuals with intellectual disability (ID)*'.[22,23] This sleep questionnaire has been used in individuals with ID or genetic syndromes[24–26] and assesses several types of sleep problems with their level of severity. A few specific questions concerning the DS and epilepsy were added. Sleep problems were defined according to the definition of Wiggs and Stores.[27] In part 4 the frequency of occurrence of 45 behaviors related to sleep are assessed on a 7-point Linkert scale.[24] Completed questionnaires can be evaluated by different scores: Composite Sleep Index (CSI), total score (TS) and 5 different sleep factor scores (FS). The CSI reflects the level of severity of sleep problems. This score ranges from 0 to 12 and is derived from the frequency of problems with settling, night waking, early waking and co-sleeping and the duration of settling and night waking. A CSI of $\geq$4 is an indicator of a severe sleep problem. There are 5 different factor scores[1]; snoring,[2] daytime sleepiness,[3] complaints related to sleep,[4] sleep apnea and[5] anxiety related to sleep. The FS 'complaints related to sleep' refers to movements, excessive sweating and episodes of confused behavior during sleep.

2.3. Control group

An abbreviated version of the questionnaire was conducted in an equally large group of patients with epilepsy recruited from the outpatient pediatric epilepsy clinic at the Antwerp University Hospital. Between March 2017 and June 2017 all parents (or caregivers) from children (aged above 6 months) with epilepsy were asked to participate voluntarily. The questionnaire could be completed on a tablet computer in the waiting room. Because the sleep behavior and prevalence of sleep disorders changes with age only patients aged $\leq$18 years could be included in the comparison analysis.

2.4. Data management and analysis

The anonymized data was extracted out of the Qualtrics Survey Software into IBM SPSS Statistics version 24 for statistical analysis. Prevalence (with 95% confidence interval) was assessed. To test for differences within the DS group, nonparametric tests were used since data were not normally distributed and sample sizes were relatively small. Differences between variables were calculated with Chi-square (or Fischer's Exact Test) for categorical variables and the Mann Whitney (or Kruskal Wallis) test for continuous variables. Association between different variables was studied with Spearman's rank-order correlation. To test for differences between the DS and control group we used the Mann Whitney or Chi-square test.

3. Results

3.1. Dravet Syndrome population

3.1.1. Demographics

56 (50% male) of the 66 recorded responses could be used for statistical analysis (see Table 1). The age ranged from 1 to 48 years with a mean of 13.7 y (median 11.5 y). Almost all patients (53/56) had a genetically confirmed DS diagnosis. In 91.1% a pathogenic mutation in *SCN1A* was identified and in two patients a mutation in *HCN1*.[28,29] The month before completing the questionnaire, 14.3% was seizure free but 53.6% had frequent seizures. Most parents indicated a daytime predominance (31/55), although in 43.6% more seizures were seen during the night. 34.5% had ≥2 nocturnal seizures per month. Seizure predominance at night was not related with the age ($p = 0.255$). Most patients use many anti-epileptic drugs (AED), on average 3.1, with a maximum of 5 (see supplementary material). Overall 15 different AED's were used in 30 different combinations. Comorbidities were often reported. Many patients suffer from a motor impairment (67.9%). Four patients could not turn in bed by themselves. An intellectual disability was seen in almost all patients (89.6%). Some patients (17.9%) suffered from an additional disease like folliculitis, a mitochondrial complex 1 disorder, gout or hypothyroidism. Body mass index (BMI) ranged from 11.7 to 34.9 kg/m^2.

3.1.2. Environmental factors

Patients most often sleep at home (82.6%) although this diminishes with age. Patients living in a residential setting were significantly older ($p < 0.001$). Most patients sleep alone in their bedroom (80.4%), a minority (19.6%) with their mother and/or father ($n = 10$ or 17.9%) or sibling ($n = 1$), defined as co-sleeping. There was no significant age difference between those that sleep alone or those that don't ($p = 0.148$). Approximately half of the patients (50.9%) have a nocturnal monitoring system. Interestingly, the group with a nocturnal monitoring system was significantly older than those without ($p = 0.026$).

3.1.3. Sleep problems and analysis of the CSI

All parents have a ritual for putting their children to bed. 18.5% of the caregivers regularly (i.e. ≥1 per week) have difficulties to get their children to sleep, some (7%) even daily. Most children (75.9%) fall asleep relatively easily (i.e. <30 min). Only 1 patient fulfilled the criteria for a severe settling problem, 3 patients for a mild settling problem. 60.4% of the children wake up regularly (i.e. ≥1 per week), with a mean frequency of 2 times per night. After waking up, most patients (74%) fall asleep relatively easily (i.e. <30 min). Based on the criteria, 42.9% had a mild night waking problem and 22.4% a severe night waking problem. None of the patients has a severe early waking problem. More than half of the parents find that their child wakes up refreshed, and is in a good mood in the morning. Most patients take a nap during the day, 51.9% during the week and 49% in the weekend.

The CSI could be calculated in 46 patients, of which 28.3% ($n = 13$) had a CSI ≥4, indicating a severe sleep disorder. Comparable outcomes could be seen for males and females. There was no correlation with the age. The CSI was significantly higher in patients with co-sleeping ($n = 10$), compared to those that sleep alone ($n = 36$) with a respectively median of 4.0 and 2.0 (Mann–Whitney $U = 97.5$, p 0.026 two-tailed). Seizure frequency did not influence the CSI score (both looking at the diurnal variation and specific seizure types). Patients with CSI ≥4 more often used stiripentol ($p = 0.003$). Other anti-epileptic drugs, including benzodiazepines, did not show any significant difference nor did behavioral medication. Interestingly, patients who currently use melatonin ($n = 7$) have significant higher CSI scores (Mann Whitney $U = 60$, $p = 0.032$). The presence of one of the comorbidities (more specifically respiratory problems, motor impairment or gastro-intestinal problems) was not associated with a higher CSI.

3.1.4. Types of sleep disturbances

The TS and 5 FS could be calculated in 45–61 DS patients. To compare the different FS, mean scores expressed as percentage of the maximum score were calculated (see Table 2). Within the DS group the FS daytime sleepiness had the highest mean score, followed by the FS snoring and the FS complaints related to sleep. TS and FS were not significantly different between genders. There was a significant negative correlation between the age and the FS complaints related to sleep ($r_S = -0.472$, $p = 0.001$) but not for the other FS (see Fig. 1). Patients who did not sleep alone had significant lower FS anxiety related to sleep ($p = 0.008$). There was no correlation between the BMI and FS snoring or sleep apnea.

Patients taking stiripentol had higher FS daytime sleepiness ($p = 0.05$), without effect on the other FS. There was no correlation between the FS daytime sleepiness and the number of AED ($p = 0.087$). Patients who took topiramate or methylphenidate had a significant lower FS daytime sleepiness (respectively $p = 0.018$ and $p = 0.019$). Patients who took CBD seemed to have a higher FS anxiety related to sleep ($p = 0.024$) although number of patients was small. Other AEDs didn't influence the FS.

3.1.5. Parental perception and impact of sleep problems

When caregivers were asked 'Do you think your child has a sleep problem at this time?', without providing criteria or definition of a sleep problem, 22/52 (42.3%) responded 'yes'. Parents described the sleep problems mainly as night waking problems (77.3%), sleepiness during the day (40.9%) and waking up early (31.8%). In more than 70%, the sleep problems were present for over a year. The findings of the parents corresponded well with the CSI with a significantly higher CSI in the group where parents indicated a sleep problem ($p = 0.001$). Most of the parents (61.5%) never received any advice or treatment for their child's sleep problems. If they received advice, this appeared to be not or partial effective in more than 90%. 31.4% of the children (16/51) received pharmacologic therapy, most often melatonin ($n = 9$) but also antihistamines ($n = 4$), benzodiazepines ($n = 2$) or CBD ($n = 1$) were prescribed. Only 2 families received cognitive-behavioral therapy or pedagogic advice, both with limited or no effect.

Parents indicated in 46% that the sleep problems had a negative influence on their life, more specific they led to

Table 1 – Participants characteristics and prevalence of sleep disorders.

	Total DS population (n = 56)	Total control population (n = 66)
Male/Female	50%/50% (28/28)	54.5%/45.5% (36/30)
Age		
Mean (SD)	13.6 y (10.5)	8.6 y (5.3)
Median (range)	11.5 y (1–48)	8.1 y (0.6–20)
Age groups		
6 m–2 y	10.7% (6/56)	19.7% (13/66)
3–6 y	25.0% (14/56)	21.2% (14/66)
7–12 y	16.1% (9/56)	39.4% (26/66)
13–18 y	23.2% (13/56)	16.7% (11/66)
19–25 y	10.7% (6/56)	3.0% (2/66)
26 y+	14.3% (8/56)	0% (0/66)
Questionnaire completed by		
Mother	83.9% (47/56)	77.3% (51/66)
Father	12.5% (7/56)	21.2% (14/66)
Other	3.6% (2/56)	1.5% (1/66)
Living situation		
Family	82.1% (46/56)	100% (66/66)
Residential facility	17.9% (10/56)	0% (0/66)
Level of cognitive functioning		
No ID (IQ > 70)	8.9% (5/56)	40.9% (27/66)
ID	76.8% (43/56)	43.9% (29/66)
Mild ID	9.3% (4/43)	13.79% (4/29)
Moderate ID	18.6% (8/43)	6.90% (2/29)
Severe ID	32.6% (14/43)	13.79% (4/29)
Profound ID	11.6% (5/43)	10.34% (3/29)
ID level not known	27.9% (12/43)	55.17% (16/29)
Unknown	14.3% (8/56)	15.2% (10/66)
Epilepsy features (based upon the seizures during the last month)		
Presence of seizure types		
(Atypical) Absences	75.0% (42/56)	62.1% (41/66)
Tonic-Clonic	69.6% (39/56)	34.8% (23/66)
Clonic/Myoclonic	58.9% (33/56)	40.0% (26/65)
Tonic	48.2% (27/56)	28.8% (19/66)
Status Epilepticus	12.5% (7/56)	16.7% (11/66)
Other seizure types	14.3% (8/56)	0.3% (2/66)
Seizures day or night time?		
Mainly nocturnal seizures	43.6% (24/55)	21.0% (13/62)
Seizure control		
Seizure free with medication	14.3% (8/56)	54.5% (36/66)
Monitoring for nocturnal seizures		
Co-sleeping	19.6% (11/56)	39.4% (26/66)
Nocturnal monitoring device	50.9% (27/53)	4.5% (3/66)
Type		
Baby monitor	26.4% (14/53)	3% (2/66)
Camera surveillance	39.6% (21/53)	3% (2/66)
Cardiorespiratory monitoring	17.0% (9/53)	1.5% (1/66)
Other	17.0% (9/53)	1.5% (1/66)
Parent (or caregiver)-reported sleep problems[a]	42.3% (22/52)	21.2% (14/52)
Type of problem (according caregiver)		
Night-waking problems	77.3% (17/22)	57.1% (8/14)
Daytime sleepiness	40.9% (9/22)	42.9% (6/14)
Waking up early	31.8% (7/22)	35.7% (5/14)
Settling problems	27.3% (6/22)	64.3% (9/14)
Anxiety related to sleep	13.6% (3/22)	2.4% (3/14)
Duration		
<1 month	0% (0/22)	0% (0/14)
1–3 months	9.1% (2/22)	14.3% (2/14)
3–6 months	13.6% (3/22)	7.1% (1/14)
6–12 months	4.6% (1/22)	14.3% (2/14)
>1 year	72.7% (16/22)	64.3% (9/14)
Prevalence sleep problem		
Severe settling problem[b]	1.9% (1/54)	4.5% (3/66)
Mild settling problem[b]	5.6% (3/54)	10.6% (7/66)
Severe night waking problem[b]	22.4% (11/49)	19.4% (12/62)

Table 1 – (*continued*)

	Total DS population (n = 56)	Total control population (n = 66)
Mild night waking problem[b]	42.9% (21/49)	30.6% (19/62)
CSI (median, range)	2 (0–9)	2 (0–12)
Severe sleep disorder (CSI ≥ 4) (95% CI)	28.3% or 13/46 (15%–42%)	31.1% or 1/61 (19%–43%)
Parental reported sleep quality		
QoS parents (median, range)	6.0 (0–10)	7.0 (0–10)
QoS patients (median, range)	7.0 (1–10)	8.0 (1–10)

[a] Caregivers answered 'yes' on the question '*Do you think your child currently has a sleep problem?*'
[b] Based on the criteria according Wiggs and Stores (see supplementary material).

Table 2 – Factor scores (% of max score).

	Total DS population						Total control population					
	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
FS_Snoring	45	39.5	19.8	37.1	14.3	85.7	61	41.6	28.6	31.4	14.3	100
FS_Daytime Sleepiness	50	45.6	16.4	46.4	14.3	75.0	63	39.5	22.6	35.7	14.3	89.3
FS_Complaints Related To Sleep	50	26.6	13.4	21.4	14.3	71.4	57	30.2	16.4	26.2	14.3	78.6
FS_Sleep Apnea	49	20.9	12.8	14.3	14.3	66.7	60	22.7	20.6	14.3	14.3	100
FS_Anxiety	50	20.9	11.3	14.3	14.3	61.9	64	27.6	18.3	14.3	14.3	76.2

Legend: FS, Factor Score; DS, Dravet Syndrome; SD, Standard Deviation.

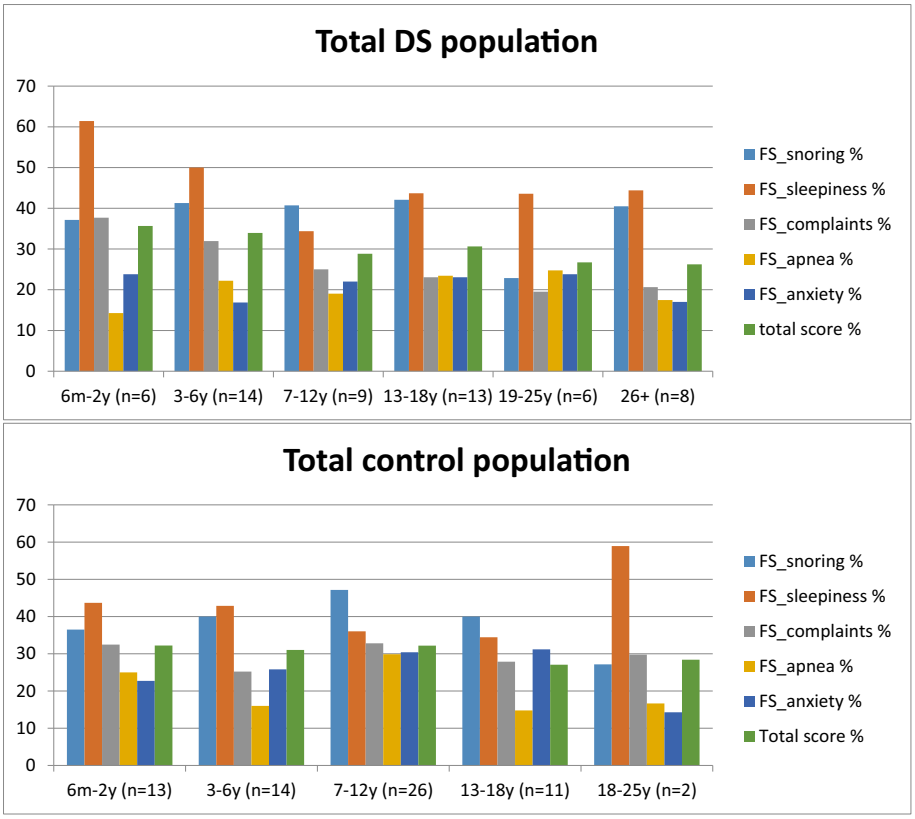

Fig. 1 – Factor and total scores (% of max) per age category. Legend: FS, Factor Score; DS, Dravet Syndrome.

awaking from sleep, sleepiness during the day, difficulties with concentration and memory and feelings of helplessness and frustration. When caregivers were asked to grade their own quality of sleep (QoS) with a number ranging from 0 to 10, with 0 being the worst and 10 the best imaginable sleep quality, the mean QoS of the caregivers was 5.9/10 (SD 2.14). The mean QoS of the patients, estimated by the caregivers, was 6.5/10 (SD 2.09). There was a significant positive correlation between the QoS of the parents and their children ($r_S = 0.43$, $p = 0.001$).

3.2. Control group

66 responses (54.5% male) were included (see Table 1). Etiology was heterogeneous ranging from absence epilepsy to Lennox Gastaut Syndrome (see supplementary material). The age ranged from 6 m to 20 y with a mean of 8.6 y (median 8.1 y). Almost all (97%) took AED's (mean number 1.8, range 0–5). In most patients, seizures appeared mainly during the day (56.5%), in 21% seizures primarily at night, and in 22.6% of them without diurnal variation. Only 4.5% of the patients used a nocturnal monitoring system.

21.2% of the parents think that their child has a sleep disorder and 31.1% of the patients had a CSI ≥4, indicating a severe sleep disorder. A mild or severe settling or night waking problem was seen in 53.2% of the patients. The TS and FS could be calculated in 65 patients, mainly showing an elevation of the FS snoring. The median parent (or caregiver)-reported personal QoS was 7.0 (mean 5.98, range 0–10), from their children 8.0 (mean 7.14; range 1–10). There was no correlation between the QoS of parents and their children.

3.3. Comparison between pediatric DS and control population

All pediatric patients (aged ≤18 y) from the control group (n = 64) and DS group (n = 42) were included in the comparison analysis (see Table 3). Age and number of patients with frequent convulsive or frequent nocturnal seizures (defined as ≥1 per week) were not significantly different between both groups. However, significant more patients from the control group were seizure free during the last month (54.7% versus 16.7%, $p < 0.001$) with a lower seizure burden in the control group. ID was also more prevalent in the DS population compared to the control group ($p = 0.001$). Motor impairment was present in approximately 60% of the patients in both groups, although significant more patients from the control group were not able to turn in their bed by themselves (14.1% (9/64) versus 2.4% (1/41) in the DS group, p 0.044). DS patients more frequently used a nocturnal monitoring system ($p < 0.00$) but co-sleeping was more common in the control group ($p = 0.04$), even if patients under the age of 2 were excluded ($p = 0.043$). Overall, there was no significant difference in percentage of children that are surveyed overnight between the DS and control group ($p = 0.186$).

Parents from DS patients reported significantly more sleep problems in their children and rated the QoS of their children significantly lower compared to the control population. If parents were asked to describe the type of sleep problem of their child, DS parents mentioned more night waking problems, and parents from the control group more settling problems (the latter being significant, p 0.03). However, based on the criteria defined by Wiggs and Stores, settling problems and night waking problems appeared equally in both populations. Nevertheless, more DS patients appeared to have a kind of sleep problem (settling problem or night waking problem, both mild or severe) compared to the control group (74.4% (29/39) versus 53.3% (32/60), p 0.036). This might be explained by the fact that more patients from the control group have a combination of different sleep problems and a tendency of more mild night waking problems in patients with DS. In both groups approximately 30% of the patients fulfilled the criteria of a severe sleep disorder (based on a CSI ≥4).

Furthermore, no significant difference could be found between the different sleep parameters (CSI, TS and FS), except for the FS daytime sleepiness. The latter being significantly more elevated in the DS population ($p = 0.042$).

4. Discussion

Concerns about sleep problems are mentioned frequently in DS patients, ranging from 58% up to 97% in the literature. In our study 'only' 42.3% of the DS parents indicated sleep problems in their child. Based on the CSI, approximately 30% of our DS patients have a severe sleep disorder, mainly night waking problems. Mild night waking or settling problems were much more common and were seen in 46.7% of the patients. Overall 69.4% of the DS patients (74.4% in pediatric DS patients) have a mild or severe (settling/night waking) problem.

The frequency of co-sleeping was surprisingly low in our study population. In a recent survey conducted in 256 parents and caregivers of patients with DS,[5] 82% of the patients slept with someone else. In our DS cohort only 19.6% of the patients slept together with their parents or sibling. It is known that environmental factors, like co-sleeping, have an influence on the (parental-reported) sleep quality. On the one hand, parents who sleep together with their child may be more aware of their child's sleep problem and will therefore more easily report sleep problems. On the other hand, co-sleeping itself can have a negative influence on the child's sleep quality with greater fragmentation of night sleep and might thus even cause sleep problems. At this moment it is not known whether the higher prevalence is related to the increased awareness or is related to the increased disturbance of the child's sleep. Köse et al. showed that co-sleeping with a parent increased the risk for sleep problems in children up to 13 fold.[30] In our study however, the parental-reported sleep problems, different factor scores, settling problems and night waking problems were not significantly different between both groups. The CSI was significantly higher in the co-sleeping group but this may be explained by the fact that co-sleeping is used to calculate the CSI. Hence co-sleeping does not seem to explain the appearance of sleep problems in our study population. Although co-sleeping was not frequent, many DS patients used a nocturnal monitoring device, so up to 58.5% of our pediatric DS patients had a form of overnight supervision (comparable with our control group). The effect of nocturnal monitoring devices on sleep fragmentation is difficult to estimate since different devices are used (e.g. cardio-respiratory monitor or video monitoring) but should be less compared to co-sleeping and may give a higher detection of sleep disturbances compared to no overnight supervision. Most DS parents sleep together with their child due to fear of SUDEP or nocturnal seizures and rarely because of sleep problems. Due to the lack of a reliable (nocturnal) seizure detection devices parents may miss nocturnal seizures while sleeping in a different room.[31]

It is known that the circadian rhythm of seizures in patients with DS tends to shift with age. Starting from late

Table 3 – Comparison analysis between pediatric DS and control group.

	Pediatric DS population (n = 42)	Pediatric control population (n = 64)	p-value (level of significance)[a]
Mean age (median; range)	8.7 y (7.0; 1–18)	8.2 y (7.8; 1–18)	0.665
Gender (% females)	45.2% (19/42)	43.8% (28/64)	0.880
Presence of motor impairment	59.5% (25/42)	60.9% (39/64)	0.884
Frequent nocturnal seizures[b]	14.6% (6/41)	19% (12/63)	0.561
Frequent convulsive seizures[c]	23.8% (10/42)	23.4% (15/64)	0.965
Seizure free during the last months	16.7% (7/42)	54.7% (35/64)	<0.001*
Overnight supervision	58.5% (24/41)	45.3% (29/64)	0.186
Co-sleeping	21.4% (9/42)	40.6% (26/64)	0.04*
Nocturnal monitoring device	43.9% (18/41)	4.7% (3/64)	<0.001*
Parent (or caregiver)-reported sleep problems[d]	42.5% (17/40)	20.3% (13/64)	0.015*
Type of problem (according parents)			
Night-waking problems	76.5% (13/17)	61.5% (8/13)	0.376
Daytime sleepiness	41.1% (7/17)	38.5% (5/13)	0.880
Waking up early	41.1% (7/17)	38.5% (5/13)	0.880
Settling problems	29.4% (5/17)	69.2% (9/13)	0.03*
Anxiety related to sleep	17.6% (3/17)	23.1% (3/13)	0.713
Duration			
<1 month	0% (0/17)	0% (0/13)	
1–3 months	11.8% (2/17)	15.4% (2/13)	
3–6 months	11.8% (2/17)	7.7% (1/13)	
6–12 months	5.9% (1/17)	7.7% (1/13)	
>1 year	70.6% (12/17)	69.2% (9/13)	
Parental reported sleep quality			
QoS of parents/caregivers[g]	6.00 (0–10)	7.0 (0–10)	0.272
QoS of children[g]	7.00 (1–10)	8.0 (1–10)	**0.011***
Total and factor scores			
Total score[g]	94.0 (59–138), n = 39	77.5 (49–169), n = 63	0.195
FS_Snoring[g]	414.0 (5–30), n = 36	10.5 (5–35), n = 59	0.603
FS_Daytime Sleepiness[g]	13.0 (4–21), n = 38	9.5 (4–24), n = 61	**0.042***
FS_Complaints Related To Sleep[g]	11.0 (6–30), n = 39	10.5 (6–33), n = 55	0.819
FS_Sleep Apnea[g]	3.0 (3–11), n = 38	3.0 (3–21), n = 58	0.360
FS_Anxiety[g]	3.0 (3–9), n = 38	3.0 (3–16), n = 62	0.131
Prevalence of sleep problems			
CSI (range)[g]	3.0 (0–7), n = 36	1.5 (0–8), n = 59	0.187
Severe sleep disorder (CSI ≥4)	33.3% (12/36)	32.2% (19/59)	0.909
Severe settling problems[e]	2.4% (1/41)	4.7% (3/64)	0.557
Mild settling problems[e]	7.3% (3/41)	10.9% (7/64)	0.538
Severe night waking problems[e]	20.5% (8/39)	20.0% (12/60)	0.950
Mild night waking problems[e]	48.7% (19/39)	30.0% (18/60)	0.060
% of patients with a (mild or severe) settling and/or night waking problem[e,f]	74.4% (29/39)	53.3% (32/60)	**0.036***

[a] P value obtained for assessing significant differences between the two treatment arms in relation to baseline characteristics and sleep behavior (Mann–Whitney test used for continuous variables and chi-square test for categorical variables); * indicates a significant p value of <0.05.
[b] Percentage of parents that indicated that their child had ≥1 nocturnal seizure per week.
[c] Percentage of parents that indicated that their child had ≥1 convulsive seizure (i.e. tonic-clonic, tonic, clonic, myoclonic, drop attack or focal with motor component) per week.
[d] Caregivers answered 'yes' on the question 'Do you think your child currently has a sleep problem?'
[e] Based on the criteria according Wiggs and Stores (see supplementary material).
[f] Patients with any kind of sleep problem (settling problem or night waking problem, both mild or severe) were added together. If patients had a settling problem and a night waking problem they were only counted once.
[g] Median score (range).

childhood nocturnal seizures appear (mainly short tonic, tonic-vibratory or tonic-clonic) often associated with a decrease in seizures during wakefulness. These nocturnal seizures often occur in clusters and have a negative influence on the QoS with frequent awakening.[32] In our cohort there is no clear increase in night waking problems with age.

Parents from DS patients reported more sleep problems and rated their child's sleep quality much lower compared to parents from the control group. This may be explained by the fact that DS patients have more daytime sleepiness and tend to have more (mild) night waking problems. In addition more patients from the control group seem to have a combination of settling and night waking problems. Patients using stiripentol tended to have more frequently severe sleep problems, in particular more daytime sleepiness. This effect was not seen with other AED's. Although the sample of patients with

stiripentol was small (n = 14) and only concerned DS patients, it will be important to further study the effect of AED's on sleep disturbances and sleep problems. This has been illustrated by Nabbout et al. were they defined a set of five patient- and caregiver-relevant outcomes that should be measured in DS clinical trials, extending the seizure efficacy.[33] One of the concepts was the impact on daily activities of the child, including somnolence and sleep disturbances. Given the negative impact from daytime sleepiness on daily functioning, it will be important to better understand the impact of the different AED's and their combinations.

The reason for the difference in sleep problems is probably multifactorial. It is well known that taking care of a child with a DS is challenging.[34] Patients with a DS do not only have epilepsy but many other non-epileptic manifestations like behavioral problems, cognitive impairment and physical limitations.[3] The high seizure burden and the elevated risk for SUDEP compared to the overall epilepsy population are responsible for the fact that more caregivers experience feelings of fear compared to the control group. These factors may influence the higher perception of sleep problems and might partially explain the lower QoS in the DS group.

In both groups, the sleep problems had a negative effect on the caregivers, not only on their QoS but also on their general well-being and performance during the day. Since the high prevalence and the negative impact it is surprising that the majority of the parents or caregivers never received any advice or treatment concerning the sleep problems of their child. Since medication did not seem to have a good effect in our patients, behavioral treatment might give better results but is not studied in patients with DS.

Our study is the first to explore the prevalence and nature of sleep disorders in patients with a DS based on the SQ-SP sleep questionnaire. This questionnaire was used because it has been studied and validated (part 4) in patients with an ID. Recently Licheni et al. used the sleep disturbance scale for children (SDSC) to investigate the prevalence of sleep problems in a cohort of DS patients. Seventy-five percent of their DS patients had sleep problems, corresponding with the 74.4% of our pediatric DS patients (or 69.4% in all DS patients) with a mild or severe night waking problem and/or settling problem. The SDSC consists of 26 items with different factor scores, making it difficult to compare our results. In the SDSC, for example, settling and night waking problems are put together in one score (disorders of initiating and maintaining sleep). However, in the article Licheni et al. indicate that 46% (26/57) of their patients woke more than twice for at least one night per week, which is in line with the mild night waking problems in our paper. The settling problems are more difficult to compare since the duration of the time it takes to fall asleep is not indicated in the SDSC. An advantage of our paper is the fact that we could define the percentage of patients with a serious sleep problem which seems to correspond in a greater degree with the parent- or caregiver reported sleep problems and have a more profound negative impact on the daily family life in our cohort of patients.

Although this paper broadens our knowledge about one of the non-epileptic manifestations in patients with DS, this study has several limitations. As with all online questionnaires, the responses are given by the caregiver and questions may be misinterpreted by the caregivers. The call for participation for DS parents was distributed through a newsletter of the Dutch Dravet foundation and may therefore not have reached all parents from DS children living in the Netherlands and Flanders. Caregivers with higher socio-economic status or those that experience sleep problems can be overrepresented. Although the clinical diagnosis of a DS syndrome was a requisite, this could not be validated by the physician. Due to the extent of the questionnaire, not all questions were answered by all participants, which may have influenced the subanalysis of the different sleep problems and sleep disturbances. Additionally, the control group was quite heterogeneous ranging from patients with very treatment resistant epilepsies like Lennox-Gastaut Syndrome to patients with a more pharmacoresponsive epilepsy. However, due to the variability in the control group they nicely represent the whole spectrum of childhood epilepsies.

Based on this exploratory study, severe sleep problems occur as often in children with epilepsy as patients with DS. However daytime sleepiness and parental-reported sleep quality are worse in DS patients. The tendency to a higher occurrence of mild night waking problems in DS patients may be related to (missed) nocturnal seizures and might explain the lower QoS. This study provides important results and may guide further research. It will be important to expand the study population and gain more insight in the role of nocturnal seizures, the effect of the different antiepileptic drugs (like stiripentol) and the effect of treatment of sleep disturbances.

Conflicts of interest

None.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2018.09.012.

REFERENCES

1. Guerrini R. Dravet syndrome: the main issues. *Eur J Paediatr Neurol* 2012;**16**(Suppl. 1):S1–4.
2. Wu YW, Sullivan J, McDaniel SS, Meisler MH, Walsh EM, Li SX, et al. Incidence of Dravet syndrome in a US population. *Pediatrics* 2015;**136**(5):e1310–5.
3. Gataullina S, Dulac O. From genotype to phenotype in Dravet disease. *Seizure* 2017;**44**:58–64.
4. Scheffer IE. Diagnosis and long-term course of Dravet syndrome. *Eur J Paediatr Neurol* 2012;**16**(Suppl. 1):S5–8.
5. Villas N, Meskis MA, Goodliffe S. Dravet syndrome: characteristics, comorbidities, and caregiver concerns. *Epilepsy Behav* 2017;**74**:81–6.
6. Bender AC, Morse RP, Scott RC, Holmes GL, Lenck-Santini PP. SCN1A mutations in Dravet syndrome: impact of interneuron dysfunction on neural networks and cognitive outcome. *Epilepsy Behav* 2012;**23**(3):177–86.
7. Grigg-Damberger MM, Foldvary-Schaefer N. Primary sleep disorders in people with epilepsy: clinical questions and answers. *Child Adolesc Psychiatr Clin N Am* 2015;**24**(1):145–76.
8. Ekinci O, Okuyaz C, Gunes S, Ekinci N, Kalinli M, Tan ME, et al. Sleep problems in pediatric epilepsy and ADHD: the impact of comorbidity. *Epilepsy Behav* 2017;**71**(Pt A):7–12.
9. Knupp KG, Scarbro S, Wilkening G, Juarez-Colunga E, Kempe A, Dempsey A. Parental perception of comorbidities in children with Dravet syndrome. *Pediatr Neurol* 2017 Nov;**76**:60–5.
10. Licheni SH, McMahon JM, Schneider AL, Davey MJ, Scheffer IE. Sleep problems in Dravet syndrome: a modifiable comorbidity. *Dev Med Child Neurol* 2017.
11. Skluzacek JV, Watts KP, Parsy O, Wical B, Camfield P. Dravet syndrome and parent associations: the IDEA League experience with comorbid conditions, mortality, management, adaptation, and grief. *Epilepsia* 2011;**52**(Suppl. 2):95–101.
12. Nolan KJ, Camfield CS, Camfield PR. Coping with Dravet syndrome: parental experiences with a catastrophic epilepsy. *Dev Med Child Neurol* 2006;**48**(9):761–5.
13. Dhamija R, Erickson MK, St Louis EK, Wirrell E, Kotagal S. Sleep abnormalities in children with Dravet syndrome. *Pediatr Neurol* 2014;**50**(5):474–8.
14. Kalume F, Oakley JC, Westenbroek RE, Gile J, de la Iglesia HO, Scheuer T, et al. Sleep impairment and reduced interneuron excitability in a mouse model of Dravet syndrome. *Neurobiol Dis* 2015;**77**:141–54.
15. Papale LA, Makinson CD, Christopher Ehlen J, Tufik S, Decker MJ, Paul KN, et al. Altered sleep regulation in a mouse model of SCN1A-derived genetic epilepsy with febrile seizures plus (GEFS+). *Epilepsia* 2013;**54**(4):625–34.
16. Grone BP, Qu T, Baraban SC. Behavioral comorbidities and drug treatments in a zebrafish scn1lab model of Dravet syndrome. *eNeuro* 2017;**4**(4).
17. Chan B, Cheong EY, Ng SF, Chan YC, Lee QU, Chan KY. Evaluation of sleep disturbances in children with epilepsy: a questionnaire-based case-control study. *Epilepsy Behav* 2011;**21**(4):437–40.
18. Parisi P, Bruni O, Pia Villa M, Verrotti A, Miano S, Luchetti A, et al. The relationship between sleep and epilepsy: the effect on cognitive functioning in children. *Dev Med Child Neurol* 2010;**52**(9):805–10.
19. Verbeek NE, Wassenaar M, van Campen JS, Sonsma A, Gunning B, Knoers N, et al. Seizure precipitants in Dravet syndrome: what events and activities are specifically provocative compared with other epilepsies? *Epilepsy Behav* 2015;**47**:39–44.
20. Jensen MP, Liljenquist KS, Bocell F, Gammaitoni AR, Aron CR, Galer BS, et al. Life impact of caregiving for severe childhood epilepsy: results of expert panels and caregiver focus groups. *Epilepsy Behav* 2017;**74**:135–43.
21. Kearney J. Sudden unexpected death in Dravet syndrome. *Epilepsy Curr* 2013;**13**(6):264–5.
22. Simonds JF, Parraga H. Prevalence of sleep disorders and sleep behaviors in children and adolescents. *J Am Acad Child Psychiatry* 1982;**21**(4):383–8.
23. Wiggs L, Stores G. Severe sleep disturbance and daytime challenging behaviour in children with severe learning disabilities. *J Intellect Disabil Res* 1996;**40**(Pt 6):518–28.
24. Maas AP, Didden R, Korzilius H, Braam W, Collin P, Smits MG, et al. Psychometric properties of a sleep questionnaire for use in individuals with intellectual disabilities. *Res Dev Disabil* 2011;**32**(6):2467–79.
25. Maas AP, Grossfeld PD, Didden R, Korzilius H, Braam WJ, Smits MG, et al. Sleep problems in individuals with 11q terminal deletion disorder (Jacobsen syndrome). *Genet Couns* 2008;**19**(2):225–35.
26. Maas AP, Didden R, Korzilius H, Braam W, Smits MG, Curfs LM. Sleep in individuals with Cri du Chat syndrome: a comparative study. *J Intellect Disabil Res* 2009;**53**(8):704–15.
27. Wiggs L, Stores G. Behavioural treatment for sleep problems in children with severe learning disabilities and challenging daytime behaviour: effect on sleep patterns of mother and child. *J Sleep Res* 1998;**7**(2):119–26.
28. Nava C, Dalle C, Rastetter A, Striano P, de Kovel CG, Nabbout R, et al. De novo mutations in HCN1 cause early infantile epileptic encephalopathy. *Nat Genet* 2014;**46**(6):640–5.
29. Steel D, Symonds JD, Zuberi SM, Brunklaus A. Dravet syndrome and its mimics: beyond SCN1A. *Epilepsia* 2017.
30. Kose S, Yilmaz H, Ocakoglu FT, Ozbaran NB. Sleep problems in children with autism spectrum disorder and intellectual disability without autism spectrum disorder. *Sleep Med* 2017;**40**:69–77.
31. Van de Vel A, Cuppens K, Bonroy B, Milosevic M, Jansen K, Van Huffel S, et al. Non-EEG seizure detection systems and potential SUDEP prevention: state of the art: review and update. *Seizure* 2016;**41**:141–53.
32. Losito E, Kuchenbuch M, Chemaly N, Laschet J, Chiron C, Kaminska A, et al. Age-related "sleep/nocturnal" tonic and tonic clonic seizure clusters are underdiagnosed in patients with Dravet syndrome. *Epilepsy Behav* 2017;**74**:33–40.
33. Nabbout R, Auvin S, Chiron C, Irwin J, Mistry A, Bonner N, et al. Development and content validation of a preliminary core set of patient- and caregiver-relevant outcomes for inclusion in a potential composite endpoint for Dravet syndrome. *Epilepsy Behav* 2018;**78**:232–42.
34. Brunklaus A, Dorris L, Zuberi SM. Comorbidities and predictors of health-related quality of life in Dravet syndrome. *Epilepsia* 2011;**52**(8):1476–82.