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Sleep problems in Dravet syndrome: a modifiable comorbidity

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ABBREVIATION

OSA Obstructive sleep apnoea

AIM Many children with severe developmental and epileptic encephalopathies experience significant sleep disturbance, causing major disruption to the family's quality of life. We aimed to determine the frequency and nature of sleep problems in individuals with Dravet syndrome.

METHODS The Sleep Disturbance Scale for Children and a seizure questionnaire were distributed to the parents/guardians of 96 patients with Dravet syndrome. Sixteen patients had two nights of home oximetry.

RESULTS Fifty-seven out of 96 questionnaires were completed. Forty-three out of 57 (75%) individuals had sleep problems. Twenty-five out of 57 (44%) individuals had an abnormal total sleep score, with difficulty initiating and maintaining sleep (22 out of 57, 39%), sleep–wake transition disorders (20 out of 57, 35%), and sleep breathing disorders (19 out of 57, 33%). Twenty-two out of 57 (39%) individuals took medication to assist sleep, predominantly melatonin (*n*=14). Thirty out of 57 (53%) recently had nocturnal seizures. Overnight oximetry showed 14 out of 16 (88%) had a higher oxygen desaturation index (>3%), and six out of 16 (38%) higher mean pulse rates, than normative values. Home oximetry was normal or inconclusive in all patients.

INTERPRETATION Seventy-five per cent of individuals with Dravet syndrome had sleep problems, highlighting the importance of routinely assessing sleep and initiating appropriate behavioural and pharmacological interventions to improve the patient and family's quality of life. A high oxygen desaturation index and mean pulse rates on pulse oximetry may reflect unrecognized nocturnal seizures.

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What this paper adds

- More than 70% of patients with Dravet syndrome have sleep problems.
- Difficulty initiating and maintaining sleep was commonest, particularly in those older than 20 years.
- Second commonest were sleep–wake transition disorders, affecting more than 50% of those younger than 5 years.
- Sleep breathing disorders were a frequent problem across all age groups.
- Oximetry was not diagnostic of sleep-disordered breathing or obvious seizures.

[Main text]

Dravet syndrome is a developmental and epileptic encephalopathy with an incidence of 1 in 22 000 to 40 000 individuals.[1] It typically presents with hemiclonic or generalized febrile status epilepticus at a mean age of 6 months.[1] Although development is normal in the first year of life, it plateaus in the second year followed by intellectual disability and sometimes behavioural problems.[1] Autistic features are observed in up to 62% of cases.[2] Between 1 years and 5 years, additional seizure types emerge including focal, myoclonic, and absence seizures; seizures are typically pharmaco-resistant.[1] Dravet syndrome has a high mortality rate,[1] with 50% to 60% of deaths being due to sudden unexpected death in epilepsy, which typically occurs during sleep.[3] More than 80% of individuals with Dravet syndrome have a mutation in *SCN1A*, the gene encoding the α1-subunit of the neuronal sodium channel $Na_v1.1$; 90% of mutations arise de novo.[4]

In children with epilepsy, sleep is one of the most important determinants of quality of life, and sleep problems have profound effects on the coping mechanisms of the entire family.[5] Poor sleep can lead to daytime behavioural problems and poor

attention, which contribute to social and academic difficulties. A bidirectional relationship exists between sleep and epilepsy, whereby having epilepsy may lead to poor quality sleep[6] and in turn sleep deprivation often exacerbates seizures.

We aimed to characterize the frequency and nature of sleep disturbance in individuals with Dravet syndrome, and to assess the possible role of unrecognized seizures in those experiencing sleep problems.

METHOD

We identified all patients with Dravet syndrome recruited to our Epilepsy Genetics Research Program who lived in Australia. We reviewed their medical history, comorbidities, and *SCN1A* mutation status. Information about seizure control and medications including sleep medications was obtained from families.

Sleep questionnaire

We asked parents/guardians to complete a questionnaire about the individual's sleep pattern in person or by mail. The Sleep Disturbance Scale for Children is a parent-reported 26-item Likert scale questionnaire designed to identify children with disturbed sleep in the previous 6 months.[7] The items in the questionnaire pertained to six categories of childhood sleep disorders: (1) disorders of initiating and maintaining sleep (seven items), (2) sleep breathing disorders (three items), (3) disorders of arousal (three items), (4) sleep–wake transition disorders (six items), (5) disorders of excessive somnolence (five items), and (6) sleep hyperhidrosis (two items), which describes excessive sweating during sleep. Questionnaires were scored according to the Sleep Disturbance Scale for Children protocol, resulting in pathological or non-pathological category scores and a 'total sleep score'. The total sleep score sums the category scores and provides an overall evaluation of sleep. Single-item responses scoring ≥3 were also considered positive as this indicated that the problem was experienced more than once or twice a week. While the Sleep Disturbance Scale for Children has not been validated in individuals older than 20 years, adults were included in our analysis as we wanted to review the impact of sleep problems in Dravet syndrome throughout life.

Descriptive statistics were used to determine the frequency of children with pathological sleep scores and to evaluate the relationship between *SCN1A* status, use of sleep medications, seizures, and sleep scores. The characteristics of the respondents and non-respondents were analysed using χ^2 testing to determine possible reasons for non-response. We reviewed age, location of residence (Victorian state or non-Victorian), and contact with the investigators in the 6 months before questionnaire distribution.

Pulse oximetry

Owing to restricted resources, a subgroup of patients was invited to have two nights of home oximetry; they were selected because of a history of sleep disturbance. Parents were instructed on the use of the Massimo Radical 7 oximeter. Oximetry was performed over two consecutive nights, with the sensor placed on the child's big toe. The oximeter was set to record oxygen saturation (SpO_2) and pulse rate values every 2 seconds. Data were downloaded using VisiDownload software (Stowood Scientific Instruments, Oxford, UK). The mean oxygen saturation, lowest SpO_2, and number of desaturation events more than 3% per hour, as well as the mean, minimum, and maximum pulse rate and the standard deviation of the pulse rate, were analysed. Data from both nights were averaged before being compared with normative data for the corresponding age group to determine whether they fell within the normal range (10th–90th centiles).[8] The trend graphs were reviewed by a paediatric sleep physician to see whether any traces met the McGill criteria for paediatric obstructive sleep apnoea (OSA) as described by Brouillette et al.[9]

Standard protocol approvals, registrations, patient consents

Ethical approval was obtained from the Austin Health Human Research Ethics Committee (H2007/02961). Written informed consent was provided by the patient or their parents or legal guardians in the case of minors or those with intellectual disability.

RESULTS

Sleep questionnaire

Complete questionnaires were returned by the families of 57 out of 96 (59%) individuals with Dravet syndrome. The patients' mean age was 14 years (range 2–36y) and 12 were older than 20 years; 27 out of 57 were female. Fifty-one out of 57 (89%) had an *SCN1A* mutation; 48 arose de novo, two were siblings whose father was mosaic for the mutation, and one was an infant whose mother also had Dravet syndrome. One questionnaire was returned incomplete.

Recent contact between the investigators and the respondents had occurred in the previous 6 months before this study for 42 out of 57 (74%), compared with only six out of 38 (16%) of the non-respondents ($p=3.22 \times 10^{-8}$). Thirty-five out of 57 (61%) respondents were from the state of Victoria, where the investigators are located, compared with seven out of 38 (18%) non-respondents ($p=3.59 \times 10^{-5}$). The mean age of the respondent and non-respondent groups was similar: 13 years 11 months and 14 years 7 months.

Forty-three out of 57 (75%) individuals had at least one abnormal category score or total sleep score. Table I shows the frequency of individuals with pathological total and category sleep scores. Twenty-four out of 25 (96%) with a pathological total sleep score had an *SCN1A* mutation.

Single question response analysis showed that, on at least one night per week, 26 out of 57 (46%) individuals woke more than twice and 27 out of 57 (47%) had difficulty falling asleep. Thirty (53%) individuals snored and daytime sleepiness was reported in 33 (58%). Pathological sleep–wake transition disorders scores were heavily weighted by positive responses to questions about the occurrence of frequent jerks (16 out of 20) and nocturnal hyperkinesia (19 out of 20).

The nature of the sleep problems differed according to the age of the patient (Fig. 1). The most common sleep problem in adults (>20y) was disorders of initiating and maintaining sleep (eight out of 12, 67%) while sleep–wake transition disorders was most frequent in children under 5 years (six out of 11, 55%). In contrast, sleep breathing disorders and disorders of excessive somnolence were most frequent for children aged 5 to 10 years, each affecting five out of 12 (42%) individuals. Two children with an abnormal sleep breathing disorder score had a vagal nerve stimulator in situ.

Twenty-two individuals (39%) took medication to assist with sleep, predominantly melatonin (*n*=14). Parents also used clonidine, trimeprazine, iron, risperidone, clobazam, fluoxetine, and 'medicinal' cannabis. Despite taking medication, 15 individuals had a pathological total sleep score and nine still had disorders of initiating and maintaining sleep. Conversely, of the 22 individuals who had disorders of initiating and maintaining sleep, only nine were on medication with four on melatonin. Only two of the 35 individuals not taking any medication to assist with sleep had previously tried and ceased melatonin therapy owing to inefficacy.

Over half (30 out of 57, 53%) of the patients had recognized nocturnal seizures in the previous 6 months, with 7% (*n*=4) experiencing them nightly. Of 12 out of 57 with disorders of excessive somnolence, 10 reported nocturnal seizures in the previous 6 months.

Pulse oximetry

Overnight pulse oximetry was completed on 16 patients with a mean age of 8 years 10 months (range 2–26y); nine were female. Fourteen out of 16 individuals had an abnormal total or subcategory sleep score on the Sleep Disturbance Scale for Children questionnaire. The two other children had reported symptoms of sleep disturbance in clinical letters, but these symptoms were no longer present at the time of oximetry. One child had tracheomalacia, having had two tracheostomies in the past for upper respiratory tract problems, and six children had a diagnosis of autism spectrum disorder. Other comorbidities, seizure control, and antiepileptic medications are described in Table II.

Fourteen out of 16 (88%) patients had oxygen desaturation indices (>3%), and six out of 16 (38%) had mean pulse rates higher than the normative values for age (Table III). Two patients had a haemoglobin saturation nadir that was below the normative values and one child had low mean haemoglobin saturation. All other parameters were normal. There was no evidence of diagnosable OSA or clinically concerning oxygen desaturations on oximetry traces. Only one patient reported nocturnal seizures during pulse oximetry.

DISCUSSION

Three-quarters of individuals with Dravet syndrome have recently experienced sleep disturbance, which is far greater than the sleep problems reported by 30% of families with young children in the general population[10] and general epilepsy cohorts.[11] Sleep is one of the major comorbidities that families coping with Dravet syndrome struggle to negotiate.[12] These sleep problems exacerbate issues such as increasing the likelihood of seizures due to sleep deprivation, impact on the child's learning, and effect on the family's overall quality of life.

Many possible factors contribute to the high frequency of poor sleep in Dravet syndrome. *SCN1A* mutations, found in more than 80% of cases, may contribute to sleep disruption by dysregulation of neurological sleep networks. In our cohort, 24 out of 51 individuals with an *SCN1A* mutation had a pathological total sleep score, whereas five out of six without an *SCN1A* mutation had a normal score. Mouse models of *SCN1A* mutations have shown that the $Na_v1.1$ channel encoded by *SCN1A* is expressed in cells important for sleep regulation, including the GABAergic neurons in the hypothalamus, thalamic reticular nucleus, and cortex.[13] A drug-naive *Scn1a* Dravet syndrome mouse model demonstrated impaired sleep homeostasis secondary to the loss of $Na_v1.1$ channels in the inhibitory forebrain GABAergic neurons,[14] implicating the gene's involvement in sleep disruption.

The high frequency of sleep disturbance may also be attributed to or compounded by refractory nocturnal seizures, and polypharmacy in children with Dravet syndrome. A similar frequency of sleep disturbance was observed in Rett syndrome,[15] although children with other developmental and epileptic encephalopathies need to be studied. Comorbidities, such as autistic features and developmental delay, frequently seen in children with Dravet syndrome, may also contribute to reports of high sleep disturbance in this population.[16]

Although parents of children with sleep problems may have been more willing to complete the questionnaire than those without, our overall questionnaire return rate was 59%, comparable to other studies (36%–79%).[15,17] Further analysis showed that respondents were more likely to be currently under care of clinicians at our centre and to live in the same state than the non-respondents. Therefore, ongoing engagement with the

research group explains at least in part which families elected to complete the questionnaire.

The specific nature of sleep disturbance varied. We identified disorders of initiating and maintaining sleep, sleep breathing disorders, sleep–wake transition disorders, and disorders of excessive somnolence as the most problematic. Only 9% of children demonstrated disorders of arousal, which is lower than in other studies of children with epilepsy (10%–31%).[11,17] This may be due to the cognitive inability of children with Dravet syndrome to describe nightmare occurrence. Sleep hyperhidrosis was also rare (8%).

Disorders of initiating and maintaining sleep occurred in 42% of individuals, and was the most frequently reported problem in adults aged above 20 years (67%). The high propensity to wake throughout the night may be due to altered sleep micro-architecture in children with Dravet syndrome. In a retrospective analysis of polysomnography on six children with *SCN1A* mutation-positive Dravet syndrome, there was an increase in cyclic alternating pattern, which is sometimes used as a marker of unstable sleep, in five of them.[18]

Disorders of initiating and maintaining sleep in individuals with Dravet syndrome may also originate in part from environmental factors. Children with epilepsy are more likely to co-sleep with their parents for many reasons, including parental concerns about nocturnal seizures and fear of their child dying.[6] However, co-sleeping can lead to sleep fragmentation, night awakenings, and increased anxiety. Parents may also exhibit difficulties with consistent limit setting and regular bedtime routines, leading to irregular sleep patterns and behavioural insomnia of childhood, including bedtime resistance and night-time wakings.[6]

Melatonin is a hormone produced by the pineal gland, released in response to darkness and following a circadian rhythm. It is frequently used as a hypnotic in children with neurological and developmental problems.[19] In children with epilepsy, melatonin improves sleep latency and decreases wakefulness after falling asleep.[20] In our cohort, 36% of children had taken sleep medications in the previous 6 months, predominantly melatonin. Only nine out of 22 patients with disorders of initiating and maintaining sleep took medication. Four took therapeutic doses of melatonin, suggesting more widespread

use of sleep medication may be beneficial, including in adult patients. Of the 22 individuals taking medication for sleep, nine still had disorders of initiating and maintaining sleep. As disorders of initiating and maintaining sleep in Dravet syndrome may be in part behavioural, or exacerbated by parenting practices, behavioural and sleep scheduling therapies should be considered in conjunction with the use of medications in the treatment of disorders of initiating and maintaining sleep.

One study found 3.5% of children with Dravet syndrome had OSA,[18] where there are repeated episodes of airway obstruction leading to gas exchange abnormalities and/or sleep fragmentation. OSA can be associated with refractory seizures, and treatment of OSA by adenotonsillectomy can lead to a reduction in seizure frequency and improved quality of life.[21] Thirty-two per cent of our cohort had a pathological score for sleep breathing disorders, similar to reports in typically developing children. Two of our thirty-six patients had a vagal nerve stimulator in situ, which is associated with mild OSA in one in three patients.[22]

We were keen to explore the utility of home overnight oximetry in this population as a screening tool, acknowledging that normal oximetry does not exclude OSA. Home oximetry is non-invasive and can be easily set up by the parent/caregiver with brief instructions. Often there is reluctance to investigate children with such complex problems, yet we found that home oximetry produced usable data on 31 out of 32 nights. Six of the 16 individuals who had at-home oximetry had a positive score for sleep breathing disorders, and all their recordings were negative or inconclusive for OSA. Individuals with OSA may show marked sleep fragmentation rather than oxygen desaturation, and significant OSA can be missed.[9] If oximetry is normal or inconclusive and there is ongoing parental concern, then patients should have a formal sleep study or polysomnography.

The sleep–wake transition disorders include sleep talking, rhythmic movement disorders, and hypnic jerks, and are so-named because they occur when falling asleep, or when transitioning between sleep stages. In our cohort, 20 children (35%) had sleep–wake transition disorders, with 54% of children younger than 5 years old affected. The sleep–wake transition disorder scores were heavily weighted by nocturnal hyperkinesia and frequent jerks. Nocturnal hyperkinesia may reflect high rates of periodic limb

movements of sleep or unrecognized motor seizures. Frequent hypnic jerks, which are generally considered benign, are detected by parental co-sleeping and might not indicate a sinister pathology. Conversely, they could be myoclonic seizures, which could only be distinguished with video-electroencephalogram monitoring.

Twelve out of 57 (21%) individuals had disorders of excessive somnolence. Daytime sleepiness may be secondary to the other night-time sleep problems described, or caused by seizures. Nocturnal seizures were reported in 30 out of 57 (53%) cases; indeed, 10 out of 12 children with disorders of excessive somnolence experienced nocturnal seizures. Nocturnal seizures lead to brief clinical or subclinical arousals and a disruption to circadian sleep–wake rhythms, particularly decreasing REM sleep.[23] Successful treatment of nocturnal seizures will improve sleep and reduce daytime sleepiness in children with Dravet syndrome. Conversely, antiepileptic drugs commonly used in Dravet syndrome such as topiramate, valproate, stiripentol, and clobazam can all cause sedation.

Six out of 16 (38%) patients who had at-home oximetry had increased mean pulse rates compared to the normative vlaues for age. High levels of wakefulness during the night secondary to disorders of initiating and maintaining sleep and sleep–wake transition disorders might be responsible for the increased pulse rate. The oximetry data were not trimmed to remove periods of wakefulness as this does not affect the interpretation of recordings using the McGill criteria to diagnose OSA.[24] Fourteen out of 16 (88%) individuals had a raised oxygen desaturation index (>3%), which is considered suspicious for respiratory abnormalities.[8] These findings were not due to obvious seizures as only one child had a seizure during their two nights of oximetry. Tonic–clonic and focal impaired awareness seizures can cause a decrease in arterial oxygen saturation and heart rate changes, including tachycardia or bradycardia. It is possible that these abnormalities reflect unrecognized seizures or subtle respiratory dysfunction. Since oximetry is unable to distinguish between central and obstructive apnoea, further elucidation using polysomnography would be helpful.

Cerebral, respiratory, and cardiovascular dysregulations have been implicated in the pathophysiology of sudden unexpected death in epilepsy.[3] As this typically occurs during sleep, it is possible that the sleep abnormalities identified contribute to autonomic

dysfunction, building on previous reports of reduced heart rate variability, which we did not assess.[25] Further characterization of autonomic sleep disturbances may pave the way to understanding the mechanisms underlying sudden unexpected death in epilepsy and inform preventative strategies.

Given the high frequency and impact of sleep problems, it is important to ask specifically about sleep when seeing patients with Dravet syndrome. Clinical evaluation, appropriate investigation, and active management are recommended for all individuals with Dravet syndrome who report symptoms of poor sleep. Effective management of sleep disorders and nocturnal seizures is likely to improve quality of life for the child and family, and has the potential to optimize developmental outcome and improve seizure control.

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Table I: Frequency of children with pathological total and category sleep scores

Total sleep score (%)	DIMS score	SBD score	DA score	SWTD score	SHY score	DOES score
25 (45)	22 (38)	19 (33)	5 (9)	20 (35)	4 (7)	12 (21)

DIMS, disorders of initiating or maintaining sleep; SBD, sleep breathing disorders; DA, disorders of arousal; SWTD, sleep–wake transition disorders; SHY, sleep hyperhidrosis; DOES, disorders of excessive somnolence.

Table II: Epilepsy characteristics and sleep disturbance scores of children who participated in home oximetry

Patient	Seizures per month		Nocturnal seizures	AEDs	*SCN1A* status	Comorbidities	Pathological scores on questionnaire
	Focal	GTCS					
1	0.2	1.5	+	LEV, TPM	+	Allergy	TSS, SWTD
2	1.5	0.7	−	LEV, TPM	+	−	TSS, DIMS
3	1.3	0.7	+	CLB, TPM, VPA	+	−	TSS, DIMS, SBD, SWTD, DA
4	0.2	0.7	+	STP, TPM	+	ASD	DIMS
5	0	0.2	−	CLB, ESM, TPM, VPA	-	ASD	TSS, DIMS
6	0.2	2.0	−	CLZ, ESM, LMT, STP, TPM, VPA	+	−	TSS, SBD, SWTD
7	0	1.8	−	CLB, STP, TPM, VPA	+	−	TSS, SBD, SWTD, DOES
8	0	0	−	TPM, VPA	+	−	−
9	3.8	0	+	CLB, LMT, TPM, VPA	+	ASD, aortic stenosis, scoliosis	TSS, DIMS, SBD, SWTD, DOES, DA
10	0.2	0	−	CLB, LCM, STP, TPM, VPA	+	ASD, tracheomalacia	DIMS
11	0	100	+	CLZ, TPM, VPA	+	ASD	TSS, DIMS, SWTD

12	0	12	+	CLB, STP, VPA	+	−	TSS, SBD
13	0	2.8	−	CLB, CLZ, LEV, STP, TPM	+	−	SBD, SWTD
14	0	0	−	CLB, TPM, VPA	+	ASD	−
15	0.4	0	−	LEV, TPM, VPA	+	Behavioural disturbance	DIMS, SWTD
16	0	1	−	VPA	+	−	TSS, DIMS, SWTD, DA

GTCS, generalized tonic–clonic seizure; AEDs, antiepileptic drugs; LEV, levetiracetam; TPM, topiramate; TSS, total sleep score; SWTD, sleep–wake transition disorders; DIMS, disorders of initiating and maintaining sleep; CLB, clobazam; VPA, valproate; SBD, sleep breathing disorders; DA, disorders of arousal; STP, stiripentol; ASD, autism spectrum disorder; ESM, ethosuximide; CLZ, clonazepam; LMT, lamotrigine; DOES, disorders of excessive somnolence; LCM, lacosamide.

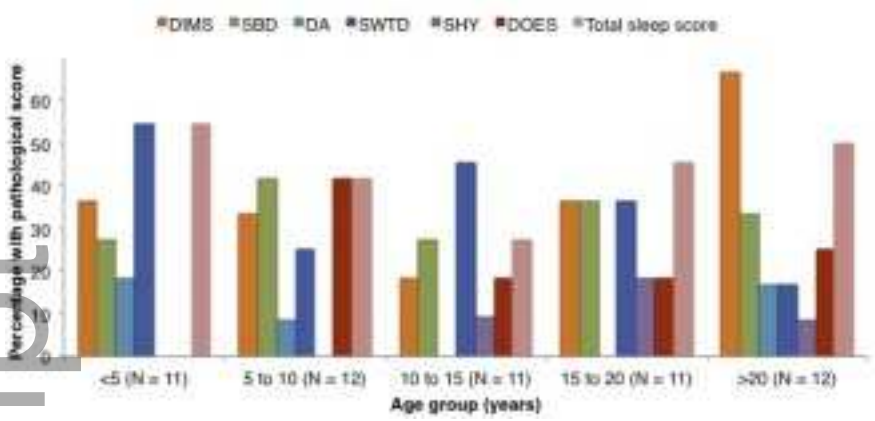
Table III: Cardiorespiratory parameters obtained by pulse oximetry during sleep

Patient	1[b]	2[b]	3[c]	4[c]	5[c]	6[c]	7[c]	8[d]
Age	2.0	2.8	3.9	4.5	4.5	4.9	5.2	7.4
Sex	M	F	F	F	F	M	F	F
Oximetry duration (h)	10.2	9.7	11.2	8.1	8.8	10.2	11.3	11.7
Desaturation index (>3%)[a]	**0.925**	**0.94**	**3.44**	0.93	**3.37**	**1.39**	**2.73**	**1.71**
Min dip SpO2 (%)[a]	91	91.5	92	93.5	86.5	90.3	**8**0	91.5
Mean SpO2 (%)[a]	98.8	98.7	97.5	98.2	**96.9**	98.6	97.5	98.4
Mean pulse rate[a]	83.77	86.94	**101.66**	80.35	89.33	71.47	86.27	**84.01**

SD pulse rate	7.55	10.14	8.03	5.96	4.85	9.58	4.64	6.86
Patient	9[d]	10[d]	11[e]	12[e]	13[e]	14[e]	15[f]	16[g]
Age	7.7	9.4	11.1	11.7	12.6	13.3	14.2	26.3
Sex	F	M	F	M	M	M	M	F
Oximetry duration (h)	9.8	10.1	10.8	6.5	9.6	10.2	7.7	9.6
Desaturation index (>3%)[a]	0.72	**0.86**	**2.98**	**0.77**	**3.53**	**1.03**	**3.53**	**0.625**
Min dip SpO2 (%)[a]	92.5	95	91.5	0	90	90.5	93.0	**89**
Mean SpO2 (%)[a]	97.6	98.5	98.2	96.5	98.8	99.0	98.2	99.1
Mean pulse rate[a]	**88.14**	82.14	**82.77**	75.55	60.31	71.38	**84.61**	**74.8**
SD pulse rate	4.90	5.59	7.91	6.98	5.65	7.37	8.44	5.335

[a]Value compared with normative values as described by Scholle et al.[8] [b]2y 2mo–3y 6mo; [c]4y 4mo–5y 10mo; [d]6y 4mo–10y 1mo; [e]9y 8mo–13y 2mo; [f]11y 5mo–15y 2mo; [g]15y 10mo–17y 11mo. Patient 3 and patient 16 fell outside these ranges, so were included in the closest age groups. Bold type indicates values lying outside the normative range for age group, defined by Scholle et al.[8]

Figure 1: Percentage of children with pathological category and total sleep score across age groups. DIMS, disorders of initiating or maintaining sleep; SBD, sleep breathing disorders; DA, disorders of arousal; SWTD, sleep–wake transition disorders; SHY, sleep hyperhidrosis; DOES, disorders of excessive somnolence.



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