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RESEARCH ARTICLE

Sleep disturbances in Norwegian children with fetal alcohol spectrum disorders (FASD) with and without a diagnosis of attention-deficit hyperactivity disorder or epilepsy

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Abstract

Background: Fetal alcohol spectrum disorder (FASD) describes a combination of developmental, cognitive, and behavioral disabilities in children with prenatal exposure to alcohol. The literature suggests that there are higher rates of sleep disturbances in these children. Few studies have investigated sleep disturbances in relation to common comorbidities of FASD. We examined the prevalence of disturbed sleep and the relationship between parent-reported sleep problems in different FASD subgroups and comorbidities like epilepsy or attention-deficit hyperactivity disorder (ADHD) and impact on clinical functioning.

Methods: In this prospective cross-sectional survey, caregivers of 53 children with FASD completed the Sleep Disturbance Scale for Children (SDSC). Information about comorbidities was collected, and EEG and assessment of IQ, daily-life executive and adaptive functioning were performed. Group comparisons and ANCOVA interaction models were used to test the associations between different sleep disturbances and clinical factors that could interfere with sleep.

Results: An abnormal sleep score on the SDSC was very common, affecting 79% of children ($n = 42$) with equal prevalence in all FASD subgroups. Difficulty falling asleep was the most common sleep problem, followed by difficulty staying asleep and waking early. The incidence of epilepsy was 9.4%, with an abnormal EEG seen in 24.5%, and a diagnosis of ADHD in 47.2% of children. The distribution of these conditions was equal in all FASD subgroups. Children with signs of sleep disturbance had poorer working memory, executive function, and adaptive functioning. Children with ADHD had a greater prevalence of sleep disturbance than those without ADHD (OR 1.36; 95% CI 1.03 to 1.79).

Conclusion: Problems with sleep are very common in FASD children and seem independent of FASD subgroup and the presence of epilepsy or a pathological EEG finding, while those with ADHD had more sleep problems. The study underscores the importance of screening for sleep disturbances in all children with FASD as these problems may be treatable.

KEYWORDS
ADHD, BRIEF, epilepsy, fetal alcohol Spectrum disorder, IQ, sleep

INTRODUCTION

Fetal alcohol spectrum disorder (FASD) is a commonly used term describing a spectrum of somatic and neurocognitive/neuropsychiatric disorders in children with prenatal exposure to alcohol (Jones & Smith, 1973). FASD may be divided into the subgroups full and partial fetal alcohol syndrome (FAS /pFAS), static encephalopathy (alcohol exposed), and neurobehavioral disorder (alcohol exposed) based on the diagnostic system the 4-Digit Code by the degree of presence of four key criteria, which include (1) growth deficiency, (2) characteristic facial features, (3) central nervous system (CNS) damage/dysfunction, and (4) level of prenatal alcohol exposure. Higher scores for each criterion indicate a diagnosis toward full FAS (Astley, 2010).

FASD is the world's leading cause of mild intellectual disability and is potentially preventable through avoidance of alcohol exposure in pregnancy (Scholin et al., 2021). Ulleland and co-workers, in the late 1960s, were among the first researchers to identify a relationship between prenatal alcohol exposure and adverse neurologic outcome (Ulleland, 1972). Today, we know that the harmful effects of alcohol on the developing brain encompass a wide range of physical and neurodevelopmental signs from the most severe condition fulfilling all criteria for the diagnosis of full FAS to less severe forms within the spectrum. The term FAS refers to individuals who have a specific set of birth defects, facial dysmorphic signs and neurodevelopmental disorders characteristic of the diagnosis (Jones & Smith, 1973). From around the year 2000, the use of the term FASD appeared including children with the absence of facial features and growth retardation, but with severe behavioral problems, hyperactivity, attention-deficit, reduced impulse control and arrested social development, even with intelligence quotient within the normal range (Rasmussen et al., 2011). There is a great variety of functioning from intellectual disability to normal cognitive functioning. The clinical picture is further complicated by significant variability in performance, difficulty learning from experience and emotional instability (Kingdon et al., 2016), but common to children with FASD is that the impairments of the central nervous system are lasting (Rasmussen et al., 2011).

Data on prevalence, especially in Scandinavia, are limited, but studies rate the prevalence in Norway at 0.5 to 1 per 1000 for FAS and at 0.5 to 1 per 100 for FASD. Based on this prevalence, the Norwegian Health Authorities estimated the incidence of FASD at 600 to 1200 children per year (H-O, 2012).

Sleep in children with FASD

Clinical evidence from parents' reports shows that children with FASD often have sleep disturbances from infancy to adolescence, a problem that seems poorly understood and investigated by healthcare providers (Ipsiroglu et al., 2013). In healthy school-aged children, disturbed sleep was reported by about 20% of parents, while children with FASD are considered much more likely to experience sleep problems with a prevalence of 50% to 80% (Goril et al., 2016). Hanlon-Dearman and colleagues found an association between FASD and reduced sleep duration and higher fragmentation of sleep (characterized by repetitive short interruptions of sleep; Hanlon-Dearman et al., 2018). Most of these earlier studies were limited by a lack of control for biasing factors such as comorbidities or poor study design (Chandler-Mather et al., 2021). Nevertheless, problems with sleep in children in general can have immense impact on quality of life for both the child and the caregivers (Ipsiroglu et al., 2013).

Polysomnography (PSG) is regarded as the gold standard for experimental sleep analyses. The use of validated children's sleep questionnaires (Bonuck et al., 2017) is another possible approach. Only three studies have measured sleep by using both instrumental examination and caregivers' questionnaires and compared it with normative data (Chen et al., 2012). Interestingly, they demonstrated that the results from sleep measurements by PSG and questionnaires are concordant with each other, which may implicate that the single use of sleep questionnaires could be sufficient (Markovich et al., 2014).

Abnormal EEG and/or epilepsy in children with prenatal alcohol/drug exposure

Both the IOM (Institute of Medicine) guidelines and the 4-Digit Code add epilepsy or documentation of recurrent nonfebrile seizures to the potential assignment of children to the diagnostic categories of FAS or PFAS (Astley, 2013; Hoyme et al., 2016). The estimated prevalence of seizures is 3% to 21% in children with FASD (Bell et al., 2010), while the prevalence of epilepsy in Norwegian children is 0.7% (Suren et al., 2013). Among healthy children without epilepsy, abnormal EEG can be found in 1% to 2%. Significantly higher incidence of abnormal EEG findings is seen in children with developmental disorders or neuropsychiatric conditions (Petruzzelli et al., 2021). The term “abnormal” refers to changes in background activity as well as more specific findings such as spikes, polyspikes, and spike-and-wave activity (Britton et al., 2016). Only a few studies have systematically examined EEG records of children with FASD, and EEG features in this patient group are poorly described (Bell et al., 2010). There are several studies, showing that such abnormal EEG activity may give lead to adverse effects on cognitive functions, concentration and attention, and possibly emotional functioning in patients with early cognitive dysfunction (Riva et al., 2013). There is no data on relationship between sleep disturbances, abnormal EEG findings, and epileptic disorders in children with FASD, but it is a well-known fact that sleep and epilepsy interact in a complex bidirectional way (Zambrelli et al., 2020). Sleep deprivation can increase seizure frequency while a higher seizure frequency can disturb sleep, which suggests that there may be a vicious cycle (Lee et al., 2021).

FASD and ADHD

According to the literature, ADHD (attention-deficit hyperactivity disorder) is one of the most common comorbidities in FASD (Fryer et al., 2007). The prevalence of ADHD in individuals with FASD is

much higher than in the general pediatric population (49% to 94% vs. 9%; Kingdon et al., 2016). A recent animal study with rodents showed that intrauterine alcohol exposure led to augmented action impulsivity while no deficits in learning or motor function were detected (Wang et al., 2021). Both ADHD and FASD are commonly associated with sleep disturbances, possibly due to shared pathophysiology (Biancardi et al., 2021), but to our knowledge, there is no data available on the comorbidity and/or prevalence of the combination of FASD, ADHD, and sleep disorders.

Study aims

The objectives of the study were to (1) examine the prevalence of sleep disturbance in a sample of 53 children with confirmed diagnoses of FAS/FASD, (2) examine the prevalence and possible differences of sleep disturbance related to FASD subgroup, (3) assess the relationship between sleep disturbance and comorbidities, and finally (4) investigate the possible impact of sleep disturbance on cognitive, executive, and adaptive functioning in children with FASD. We hypothesized that there would be an increased prevalence of sleep disturbances in children with FASD and that FASD subgroup and presence of comorbidities (ADHD/epilepsy) would have impact on sleep and any sleep disturbances. We also hypothesized reduced clinical functioning in children with sleep disturbance compared with those with normal sleep pattern.

MATERIAL AND METHODS

Study design

In this prospective cross-sectional survey, we included children and adolescents referred to the Regional Competence Center for children with prenatal alcohol/drug exposure at Sørlandet Hospital in Arendal, Norway, in 2020 to 21. All of them fulfilled an FASD diagnosis based on the 4-Digit Code after clinical assessment.

Participants

The study sample consisted of 53 children and adolescents with FASD (mean age = 10 years, SD = 3.8, age range 3 to 17 years; 63% males). Seventy-five children were multidisciplinary assessed, 55 filled the diagnostic criteria for FASD and 53 of those consented to participate. According to FASD subgroup, 24% had FAS/pFAS and 35% had static encephalopathy (alcohol exposed). Neurobehavioral disorder (alcohol exposed) was diagnosed in 41% of patients.

Demographics

Demographic information, comorbidities such as epilepsy and ADHD, and available data on prenatal alcohol exposure were mainly collected prior to admission. However, when ADHD was highly suspected in some children after the clinical assessment at our center, the children were referred back to the local child psychiatric department with the question of a diagnosis of ADHD. The local child psychiatric department then informed us about the result of their assessment. We also collected information about the use of sleep and/or antiseizure medication.

Clinical assessment

The diagnosis of FASD and FASD subgroup was based on the 4-Digit Code. All participants underwent a comprehensive standardized cognitive and neuropsychological assessment by a trained neuropsychologist and a clinical examination by a neuropediatrician with long experiences within FASD. The clinical assessment did not include specific diagnostics for ADHD, but it could lead to a recommendation to asses for ADHD at the local child psychiatric department.

1. The children were assessed cognitively with a complete version of the Wechsler Intelligence Scale for Children (WISC--IV/V; Wechsler, 2008). WISC comprises four indices: Verbal Comprehension Index, Perceptual Reasoning Index, Working Memory Index and Processing Speed Index, and Full Scale IQ. In this paper, scores on Full Scale IQ and the Working Memory Index are reported. For those older than 16 years, the Wechsler Adult Intelligence Scale (WAIS IV) was used.
2. To assess the child's daily functioning, the children were examined using the parent-reported Vineland Adaptive Behavior Scales-II. The Adaptive Behavior Composite Score, based on communication, daily living skills, and socialization, was recorded. Lower scores indicate poorer performance.
3. Executive function behaviors in home environment were evaluated by the parental-reported Behavioural Rating Inventory of Executive Function (BRIEF). Higher scores indicate poorer performance (Gioia et al., 2002).

Sleep measurement

To collect information on sleep pattern, we used the Norwegian version of the Sleep Disturbance Scale for Children (SDSC). The SDSC is a sleep-related questionnaire that has demonstrated through validation an adequate level of internal consistency, test–retest reliability, and availability of normative data (Bruni et al., 1996). All caregivers filled out the standardized sleep questionnaire. A total score of sleep disturbance and scores on its six subscales were calculated. The six subscales include DIMS = Disorders of initiating and maintaining sleep, DOES = Disorders of excessive somnolence, SBD = Disorders of sleep-related breathing, DA = Disorders of arousal, SHY = Sleep hyperhidrosis, and SWTD = Sleep–wake transition disorders. Summing up the six subdomains (with each item scored from 1 to 5) gives a total score from 26 to 130; where higher scores indicate

greater difficulties with sleeping. The general population sample's SDSC scores became our normative data for the local pediatric population and were used to calculate T-scores. In accordance with Bruni et al. (1996), we dichotomized the total score for analyses at the 75th percentile (1 = sleep disturbance ≥75th percentile, 0 = others) as cut-off, corresponding to the scale TS-total score with a cutoff level for "Has sleep disorders" at 70 points. The variable "Has sleep disorders" (Yes/No) was therefore also included in the analyses. The children were divided in two age groups, one from 3 to 6 years, and the other from 7 to 17 years, due to the fact that normal sleep patterns significantly change after the age of five. The SDSC score was compared with the caregivers' anamnestic description of disturbed sleep to the pediatrician to examine the reliability of the SDCS results.

EEG measurement

All children underwent a standardized EEG examination at Sørlandet Hospital. The EEG protocol includes a 2-h, 20-channel EEG registration using a Nicolet One EEG system by Scan-Med Norway. The EEG was consequently performed at the same time at 1 PM trying to avoid the effect of disturbed night sleep. Epilepsy and seizures were classified according to the International League Against Epilepsy Classification. A neuropediatrician was responsible for interpreting of the EEG and an electrophysiologist from the National Centre for Epilepsy in Oslo was able to provide a second opinion on controversial findings. Abnormal EEG patterns were defined according to the terminology used in the last revised glossary by the International Federation of Clinical Neurophysiology (epileptiform pattern, background slowing, and focal slowing; Kane et al., 2017). Historically, EEG (as quantitative EEG analyses) played a diagnostic role in the assessment of children with ADHD, but more recent reviews have concluded that EEG currently cannot be used as a diagnostic tool (Lenartowicz & Loo, 2014) for that purpose.

Statistics

We transferred clinical and demographic data into an electronic database and processed data using the Statistical Package for the Social Sciences (SPSS, IBM, Chicago, IL, U.S.A.), version 25.0. To test for sample distribution, we used a histogram analysis and Shapiro–Wilk test. As most of data were not distributed normally, we used nonparametric tests to determine statistically significant differences, with a significance level set to 0.05. Quantitative variables were expressed using the median and minimum and maximum. The Mann–Whitney *U* test was used for comparisons between groups of continuous variables. We used linear regression analysis to investigate whether sleep disorders (SDSC scores) were associated with FASD subgroups and comorbidities. To deal with a very small amount of missing (anamnestic) data, we used imputation of data as a reasonable guess for missing data. The odds ratios (ORs) with 95% confidence intervals (CIs) were calculated and used as an estimate of the relative risk for children with FASD and ADHD to have sleep disturbances compared with those without ADHD as comorbidity.

TABLE 1 Clinical characteristics of the study participants ($n = 53$).

Male	33 (62.3%)
Female	20 (37.7%)
Age groups	
3 to 6 years	11 (20.7%)
7 to 17 years	42 (79.3%)
Alcohol only	34 (64.2%)
Alcohol and other illegal drugs	19 (35.8%)
Living conditions	
With biological parent(s)	9 (17%)
In foster care	32 (60.4%)
Adopted	12 (22.6)
SES (Hollingshead Four-Factor Index of Socioeconomic Status)	SES 1 to 2: 17—32.1% SES 3 to 4: 36—67.9%

Ethics

The study was approved by the hospital's local Ethics Committee and by the Regional Committee for Medical and Health Research Ethics (no 2017/2404). The children's legal guardians/parents agreed to participate in the study by signing the informed consent form.

RESULTS

Clinical characteristics

Clinical characteristics of the study population are shown in Table 1. The 53 participants included 33 boys (62%) and 20 girls (38%) whose ages ranged from three to 17 years (mean age 10.1 ± 3.8 years). The children were categorized according to FASD subgroups and divided into two age groups (3 to 6 years and 7 to 17 years). Prenatal exposure to alcohol alone was confirmed in about two-thirds of the cases (64%), while exposures to both alcohol and other drugs were confirmed in about one-third (36%) of cases. Based on the 4-Digit Code, full and partial FAS/pFAS was diagnosed in 13 children (24.5%), static encephalopathy with known exposure to alcohol in 18 children (34%) and neurobehavioral disorder (alcohol exposed) in 22 (41.5%) of the children. Most of the children (33% to 62%) were in foster care, 11 were adopted (21%), and 9 (17%) were living with their biological parents. The SES (Hollingshead Four-Factor Index of Socioeconomic Status) was dichotomized, 17 children (32.1%) lived with socioeconomic status 1 to 2 and 36 (67.9%) with status 3 to 4. Thirty-three children (62%) had one or more comorbidities other than ADHD and epilepsy. The most common were eating difficulties (39.6%) and learning disorders (30.2%). The most common mental health condition was reactive attachment disorder (ICD10-F94.1) in seven children (13.2%; Table 2).

Sleep disturbance in FASD children

Based on the SDSC, disturbed sleep was very common among children with FASD, affecting 42 (79%) of the children (Table 3), with increased prevalence in all the FASD subgroups. Difficulty falling asleep and maintaining sleep (DIMS) was the most common sleep problem encountered (74%), followed by disturbed sleep–wake transition (SWTD; 70%) and disorders of arousal (DA; 59%). Sleep-related hyperhidrosis (SHY) had the lowest score (30%). In the category sleep–wake transition disorder (SWTD), only one clinical group had an increased score, that is, the 11 children already using sleep medication prior to our assessment (an antihistamine medication in two children and melatonin in nine children). Table 4 shows that the mean SDSC total T-score for the entire sample (n = 53) was 63.49, with the lowest score for the FAS/pFAS subgroup (60.69) and highest score for the neurobehavioral disorder (alcohol exposed) subgroup, but without any significant differences between the groups. Neither did we find any significant FASD subgroup differences for each of the SDSC domain scores. To examine the reliability of the SDCS results, we compared the SDSC scores to the caregivers' anamnestic description of disturbed sleep. Those who informed about sleep disturbances in the interview with the pediatrician had significantly higher SDSC T-scores than those who did not inform about problems with sleep (T-score 79 vs. 56, $p > 0.001$).

FASD and comorbidities

Table 5 presents the prevalence of ADHD and epilepsy/abnormal EEG in the whole sample and the different FASD subgroups. Of the 53 children, 25 (47%) had a confirmed ADHD diagnosis whereof six (24%) were receiving *central* nervous system *stimulants*. The highest prevalence of ADHD was seen in the static encephalopathy subgroup (55.6%), showing a trend towards significance compared with the neurobehavioral disorder group where 37% of children had ADHD (p = 0.08). Five children had epilepsy (9.4%); all of them were treated with antiseizure medications (Lamotrigine), and none was in the FAS/pFAS subgroup. Pathological EEG was found in 13 (24.5%) children including the patients with epilepsy. These pathological findings were equally distributed throughout the FASD subgroups and not overrepresented in the ADHD group (p = 0.09 in a linear regression model). Table 6 provides further details on the specific EEG findings. Even if not intended, five of the children (9.4%) fell asleep during EEG registration with an average sleep duration of 6.4 min, but not leading to additional pathological findings. Two of the nine children with epileptiform activity on EEG had generalized epileptiform discharge on EEG, while seven had focal epileptiform activity. Two children had generalized and two focal slowing on EEG background activity.

The relationship between sleep disturbances and background variables and comorbidities

In Table 7, we present the relationship between mean SDSC T-scores in the presence or absence of comorbidities like ADHD and epilepsy. Additionally, we relate SDSC scores to relevant factors such as the socioeconomic status (SES), if prenatal exposure to alcohol or the combination of alcohol and illicit drugs, or living condition, that is, if the child lived with his/her biological parents or was in foster care. We did find a significant increased risk for disturbed sleep in children with FASD + ADHD compared with children without an ADHD diagnosis (p = 0.003). A higher proportion of children with ADHD, 23 (92%) had sleep disturbances, compared with 19 children (68%) without ADHD (OR 1.36; 95% CI 1.03 to 1.79). Data demonstrated no significant relationships between sleep disturbances and age groups (p = 0.6), the comorbidity epilepsy (p = 0.23), SES (p = 0.13) or whether intrauterine exposure to alcohol only or alcohol and illegal drugs in combination (p = 0.26).

Clinical functioning in children with and without sleep disturbances

Table 8 presents neuropsychological findings in all children with FASD and in those with and without sleep disturbances. Those with disturbed sleep had inferior executive function scores and a trend toward lower working memory score (p = 0.08) and inferior general adaptive

TABLE 2 Most common comorbidities (other than ADHD and epilepsy), including mental health conditions in the study population. Diagnostic categories with <4 cases are not listed.

ICD 10 diagnostic code	Name of diagnostic category	No of children	% of children
F80	Specific developmental disorder of speech and language	4	7.5
F81	Specific developmental disorder of scholastic skills	16	30.2
F82	Specific developmental disorders of motor function	7	13.2
F43	Reaction to severe stress and adjustment disorders (PTSD included)	4	7.5
F94.1	Reactive attachment disorder	7	13.2
F98	Other behavioral and emotional disorders with onset specific to childhood and adolescence	4	7.5
F40, F41, F42, F91, F93, F95	Other mental health condition	5	9.4
E44, E66.9, R62.8, R63.3	Eating difficulties	21	39.6

Abbreviation: ADHD, attention-deficit hyperactivity disorder.

TABLE 3 Results of the SDSC total and subscales in all children with FASD and in the different FASD subgroups. T-score cutoff >70 for those with disturbed sleep.

Sleep pattern		All FASD children ($n = 53$)	FAS/pFAS ($n = 13$)	Static encephalopathy (alcohol exposed) ($n = 18$)	Neurobehavioral disorder (alcohol exposed) ($n = 22$)
Total	Disturbed	42 (79%)	9 (69%)	15 (83%)	18 (82%)
	Normal	11 (21%)	4 (31%)	3 (17%)	4 (18%)
DIMS	Disturbed	39 (74%)	9 (69%)	13 (72%)	17 (77%)
	Normal	14 (26%)	4 (31%)	5 (28%)	5 (23%)
SBD	Disturbed	30 (57%)	7 (54%)	13 (72%)	12 (55%)
	Normal	23 (43%)	6 (46%)	5 (28%)	10(45%)
DA	Disturbed	31 (59%)	8 (62%)	9 (50%)	14 (64%)
	Normal s	22 (41%)	5 (39%)	9 (50%)	8 (36%)
SWTD	Disturbed	37 (70%)	7 (54%)	12 (67%)	18 (82%)
	Normal	16 (30%)	6 (47%)	6 (33%)	4 (18%)
DOES	Disturbed	30 (57%)	8 (62%)	9 (50%)	13 (59%)
	Normal	23 (43%)	5 (38%)	9 (50%)	9 (41%)
SHY	Disturbed	16 (30%)	3 (23%)	8 (44%)	5 (23%)
	Normal s	37 (70%)	10 (77%)	10 (56%)	17 (77%)

Note: FASD subgroups are based on the FASD 4-Digit Code.

Abbreviations: DA, Disorders of arousal; DIMS, Disorders of initiating and maintaining sleep; DOES, Disorders of excessive somnolence; FAS, fetal alcohol syndrome; FASD, fetal alcohol spectrum disorder; pFAS, partial fetal alcohol syndrome; SBD, Disorders of sleep-related breathing; SDSC, Sleep Disturbance Scale for Children; SHY, Sleep hyperhidrosis; SWTD, Sleep–wake transition disorders.

function score ($p = 0.10$). Full-IQ was similar in the two groups. Those with ADHD did not differ from those without ADHD with regard to neuropsychological scores (data not shown).

DISCUSSION

The overall prevalence of sleep disturbances was very high among children with FASD, with 79% of children scoring above the SDSC cutoff for clinically significant sleep disturbances. We did not find any significant differences in the prevalence of sleep disturbances between the different FASD subgroups. Neither did our results indicate any significant relationship between sleep disturbances and age group, socioeconomic status or whether the child had been exposed to alcohol only or alcohol and illegal drugs combined. Children with sleep disturbances had inferior executive function scores. Those with diagnosed ADHD had more sleep problems than those without, while this was not the case for those with epilepsy or abnormal EEG.

Prevalence of sleep disturbances in FASD

Our study findings of 79% of FASD children scoring above the cutoff for clinically significant sleep disturbances confirm the high prevalence of sleep disorders in this group. Sleep problems did not differ according to age or FASD subgroup, underlining the need of formal sleep assessment as an integral part of the multidisciplinary diagnostic assessment for any child with FASD. Similar results are shown for children with other neurological diseases such as epilepsy (Wajszilber et al., 2018; Zambrelli et al., 2020), but the prevalence of sleep disorders seems to be even higher in FASD. Animal studies have demonstrated that intrauterine exposure to alcohol was associated with thalamic, hypothalamic, endocrinal changes, and long-term disruption in sleep–awake rhythmicity (Weinberg, 1994). Appropriate development of the thalamus and hypothalamus is vital for the control of sleep, and quantitative MR imaging studies have demonstrated volume loss of these brain structures in children with FASD (Treit et al., 2020). According to the current knowledge, children with FASD may have difficulties with different types of state regulation; sleep being one of them (Hanlon-Dearman et al., 2018). These impairments may affect sleep onset, sleep–wake cycling, and sleep hygiene. Neuronal systems that usually maintain sleep through sensory inhibition, behavioral inhibition, and neuroendocrine regulation may be compromised by prenatal exposure to alcohol (Lebel et al., 2008). The high SDSC total score for these children in our study was mainly driven by increased scores in the two domains related to difficulty falling asleep and maintaining sleep (DIMS) and sleep–wake transition (SWTD), typically described as pediatric insomnia (Owens & Mindell, 2011). This corresponds to previous research results within this patient group (Chen et al., 2012; Goril et al., 2016). If DIMS/SWTD is the main finding from a sleep medicine perspective, RLS (restless legs syndrome) as a comorbidity and/or differential diagnosis must be considered (Klingelhoefer et al., 2016). We did not perform a standardized examination regarding RLS, but asked caregiver about symptoms on "restlessness," such as "twitching/jerking/kicking off blankets." That was not the case in our patients.

TABLE 4 Mean SDSC T-scores and standard division for the whole sample and FASD subgroups.

	All children ($n = 53$)	pFAS/FAS	Static encephalopathy (alcohol exposed)	Neurobehavioral disorder (alcohol exposed)	*p*-Value
Total sleep disorders					
T-score (mean)	63.5	60.7	64.3	64.5	0.56
Standard division	14.4	15.4	14.1	14.6	
DIMS					
T-score (mean)	66.5	62.6	65.4	69.9	0.54
Standard division	19.3	16.3	15.5	19.3	
SBD					
T-score (mean)	51.7	51.5	54.6	49.6	0.18
Standard division	8.5	10.2	9.8	5.6	
DA					
T-score (mean)	60.2	60.5	59.8	60.2	0.87
Standard division	16.9	18.8	17.9	15.7	
SWTD					
T-score (mean)	60.6	58.7	59.7	62.4	0.58
Standard division	15.5	16.9	13.8	14.1	
DOES					
T-score (mean)	54.6	54.5	53.4	55.6	0.84
Standard division	11.3	12.2	11.1	11.4	
SHY					
T-score (mean)	49.8	49.1	52.9	47.7	0.36
Standard division	11.3	9.8	14.8	8.6	

Note: FASD subgroups from 4-Digit Code (Astley, 2004). Kruskal–Wallis test. The significance level is $p < 0.05$.

Abbreviations: DA, Disorders of arousal; DIMS, Disorders of initiating and maintaining sleep; DOES, Disorders of excessive somnolence; FAS, fetal alcohol syndrome; FASD, fetal alcohol spectrum disorder; pFAS, partial fetal alcohol syndrome; SBD, Disorders of sleep-related breathing; SDSC, Sleep Disturbance Scale for Children; SHY, Sleep hyperhidrosis; SWTD, Sleep–wake transition disorders.

TABLE 5 Comorbidities and FASD subgroups (from 4-Digit Code).

	All FASD children ($n = 53$)	FAS/pFAS ($n = 13$)	Static encephalopathy (alcohol exposed) ($n = 18$)	Neurobehavioral disorder (alcohol exposed) ($n = 22$)
ADHD				
Yes	25 (47%)	7 (54%)	10 (56%)	8 (36%)
No	28 (64%)	6 (46%)	8 (44%)	14 (64%)
Epilepsy				
Yes	5 (9%)	0	3 (17%)	2 (9%)
No	48 (91%)	13 (100%)	15 (83%)	20 (91%)
Pathological EEG				
Yes	13 (25%)	3 (23%)	4 (22%)	6 (27%)
No	40 (75%)	10 (77%)	14 (78%)	16 (73%)

Abbreviations: ADHD, attention-deficit hyperactivity disorder; EEG, electroencephalogram; FAS, fetal alcohol syndrome; FASD, fetal alcohol spectrum disorder; pFAS, partial fetal alcohol syndrome.

Prevalence of sleep disturbance related to FASD subgroup and exposure

Contrary to our hypothesis, no significant difference in the prevalence of sleep disturbances was found between the FASD subgroups, indicating that sleep disturbance in these children is a major problem in all FASD subgroups. Olateju et al. (2019) mentioned a relationship between prenatal alcohol exposure and the alterations of cerebral orexinergic (hypocretin) and cholinergic neurons responsible for the regulation of circadian rhythms. This, which is described as common pattern and not related to FASD subgroup, may explain the lack of differences in sleep disturbances among

TABLE 6 Specific EEG findings in the study group.

EEG findings	Number (*n*)	Percentage %	Type of epileptiform activity	*n*/%
Falling asleep during EEG registration	5/53	9.4%		
Pathological (awake)	13/53	24.5%		
Epileptiform activity	9/13	69.2%	Generalized epileptic discharges	2/9; 22%
Generalized slowing	2/13	15.5%		
Focal slowing	2/13	15.4%	Focal epileptiform activity	7/9; 78%

TABLE 7 Mean SDSC T-score and standard division related to comorbidities and relevant background variables in the study group ($n = 53$)

	n	Mean (SD)	*p*-Value
Age group			
Age 3 to 6 years	11	65.4 (15.2)	0.60
Age 7 to 18 years	42	63.0 (14.4)	
Use of sleep medicine			
Yes	11	70.2 (13)	0.19
No	42	61.7 (13.4)	
ADHD			
Yes	**25**	**66.8 (14)**	**0.003**
No	**28**	**60.5 (14.4)**	
ADHD with treatment			
Yes	6	73.2 (10.8)	0.42
No	19	64.8 (14.6)	
Epilepsy			
Yes	5	66.0 (20.4)	0.27
No	48	63.2 (14)	
Pathological EEG			
Yes	13	63.2 (15.5)	0.68
No	40	63.6 (14.3)	
SES			
SES 1 to 3	17	68.6 (15.4)	0.13
SES 3 or 4	36	61.1 (13.5)	
Exposure			
Alcohol only	34	62.5 (15.5)	0.26
Alcohol and other illegal drugs	19	65.3 (12.5)	
Living condition			
With biological parents	9	64.5 (15.2)	0.32
In foster care	32	60.4 (19.1)	

Note: Mann–Whitney *U*-test. The significance level is $p < 0.05$.

Abbreviations: ADHD, attention-deficit hyperactivity disorder; EEG, electroencephalogram; FASD, fetal alcohol spectrum disorder; SES, Hollingshead Index of Socioeconomic Status.

FASD subgroups. Children with FAS/pFAS—the most severe forms of FASD—did not have poorer sleep than children within other FASD subgroups. Neither did our results indicate any significant relationship between sleep pattern and age, socioeconomic status, or whether the child was exposed to alcohol only or combined alcohol and illegal drugs. This is in contrast to findings by Lewien et al. (2021), suggesting that lower SES and less stable caregiving was associated with increased sleep-related difficulties in healthy adolescences.

Sleep disturbance and comorbidities

The prevalence of epilepsy is 0.7% and of ADHD 2% in Norwegian children (Suren et al., 2013), while we found a prevalence by 9% and 47% in our sample of children with FASD. Additionally, we found EEG pathologies in almost 25% of the patients. Even if not intended or proceeded according to international recommendations for EEG after sleep deprivation, disturbed sleep may have influenced the EEG findings, especially in children with generalized discharges where sleep deprivation is a known trigger (Renzel et al., 2016). The prevalence of ADHD in FASD is also considered to be higher compared with the general pediatric population (47% to 94% versus 9%; Kingdon et al., 2016). In our study, 47% of the children with FASD had ADHD, which is in accordance with the results from a recent meta-analysis by Lange et al. (2018), reporting ADHD to be the most common comorbid disorder among children with FASD with a prevalence of 52.9%. The children with ADHD in our study had more sleep disturbances than those without ADHD. *Both* ADHD and FASD are commonly associated with sleep disturbances, possibly due to shared pathophysiology (Biancardi et al., 2021). Cortese et al. (2009) showed in a meta-analysis including 722 children with ADHD that these children had significantly higher scores on most of the examined sleep parameters.

Strength and weaknesses

Using a questionnaire filled out by the caregiver only to record sleep disturbances in children could be a weakness of our study. Only a few studies have evaluated sleep disturbances in FASD children using a standardized questionnaire (Chen et al., 2012), while one used polysomnography (PSG; Goril et al., 2016). Interestingly, these studies demonstrated that the results from sleep measurements by PSG and questionnaires are equivalent to each other, which may imply that the single use of questionnaires could be

TABLE 8 Clinical functioning in FASD children—all children and those with and without sleep disturbance.

	All children with FASD ($n = 53$)	FASD with disturbed sleep ($n = 42$, 79%)	FASD with normal sleep ($n = 11$, 21%)	p-Value
Full-IQ score (mean score/SD)	80.1 (12.2)	79.6 (13.2)	82.3 (8.3)	0.48
Working memory index (mean score/SD)	78.4 (10.5)	76.9 (13.3)	82.9 (4.7)	0.08
BRIEF behavior regulation index (mean/SD)	**74 (11.3)**	**76.2 (12.2)**	**67 (8.5)**	**0.008**
BRIEF metacognition index (mean/SD)	70.7 (8.6)	71.9 (8.9)	66.8 (9.7)	0.10
BRIEF general cognitive index (mean/SD)	74 (9.2)	75.8 (9.5)	68.3 (8.6)	0.02
VABS composite score (mean/SD)	59.7 (8.9)	58.5 (9.2)	63.8 (8.2)	0.10

Note: Mann–Whitney *U*-test. The significance level is $p < 0.05$.

Abbreviations: ADHD, attention-deficit hyperactivity disorder; BRIEF, Behavior Rating Inventory of Executive Function; FASD, fetal alcohol spectrum disorder; SD, standard deviation; VABS, Vineland Adaptive Behavior Scales.

sufficient when it comes to find a proper way to screen for sleeping problems (Markovich et al., 2014), as in our study. Another issue for consideration could be the high number of children in foster care referred to our center (62%). A possible weakness could be that foster care parents are less familiar with the child's usual sleeping patterns and children in foster care in general might have difficulty establishing routine sleeping patterns. However, we did not find any statistical differences in sleep problems between children in foster care and the others. In addition, the foster care children in our study had been living in the family for several years when attending this study (mean 6.7 years SD 3.2). Our results are limited to a group of 53 Norwegian children diagnosed with FASD, and as for many other studies on children, our research relies on a clinically referred sample. This may be problematic with regard to generalization of the results to all children with FASD, given that children referred to a specialized competence center as ours, are more likely to be more severely impaired, are more often recruited from foster care (as shown in the results), and have crossed a threshold where caretakers are seeking help. However, the distribution of children in the different FASD subgroups in our study is quite comparable to a much larger sample, which also included mostly clinically referred children (Astley, 2010). Strength of study is that our patients underwent a clinical assessment done by professionals within the field of FASD, and all of the children had a confirmed diagnosis of FASD based on 4-Digit Code.

Clinical implications

Different authors describe the importance of well-regulated sleep and the fact that sleep disturbance may affect several aspects such as memory, learning, cognitive flexibility, verbal functions, and attention, which are cognitive domains that may already be affected in children with FASD (Jan et al., 2010). In our study, the children with sleep disturbances had similar IQ, but inferior executive function scores and a trend toward lower working memory score ($p = 0.08$) and inferior general adaptive function score ($p = 0.10$), compared with the children without abnormal sleep. This indicates lower functioning during daytime in children with FASD. The fact that sleep problems can further exacerbate neurobehavioral and cognitive conditions, screening, and treatment of sleeping disturbance is of huge importance (Ipsiroglu et al., 2013). Even if sleep disturbances are described as a common problem in FASD children, it is often unrecognized (Chen et al., 2012; Hanlon-Dearman et al., 2018; Ipsiroglu et al., 2013). Our findings underline the need of sleep evaluation for all children with FASD and should be a reminder to healthcare providers regarding the high prevalence and severity of sleeping problems in these children. Clinicians should include a standardized assessment of sleep, and we recommend the use of SDSC to improve diagnosis and treatment. Larger samples and further research on this topic could aid to establish some guidelines that can help using the most effective methods of examination and intervention.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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