Sleep disturbances and behavioral symptoms in pediatric Sotos syndrome

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Background: Sotos syndrome (SoS) is a rare overgrowth genetic disease caused by intragenic mutations or microdeletions of the *NSD1* gene located on chromosome 5q35. SoS population might present cognitive impairment and a spectrum of behavioral characteristics, with a worse profile in patients with microdeletion. Although patients with SoS are known to have impaired sleep habits, very little data are available. The present study aimed to assess the prevalence of sleep disorders (SDs) in a pediatric cohort of patients with SoS and their correlation with neuropsychiatric profiles.

Methods: We included patients with a SoS diagnosis and age < 18 years; all patients underwent a comprehensive neuropsychological assessment, including evaluation of cognition, adaptive functions through the Adaptive Behavior Assessment System-Second Edition (ABAS-II), and behavioral problems using the Achenbach Child Behavior Checklist (CBCL) and Conners' Parent Rating Scale-Revised (CPRS-R:L) questionnaire. To investigate the presence of SD parents, the Sleep Disturbance Scale for Children (SDSC) was completed.

Results: Thirty-eight patients (M 61%, F 39%, mean age 11.1 ± 4.65 years) were included in the study. Although only two had a prior SD diagnosis, 71.1% (N=27) exhibited pathological scores on SDSC. No statistically significant associations were found between positive SDSC results and genetic microdeletion, intellectual disability (ID), or other medical conditions/treatments. However, a positive correlation emerged between SDSC scores and Conners' Global Index (*p*=0.048) and Restless/Impulsive (*p*=0.01) scores, CBCL externalizing (*p*=0.02), internalizing (p=0.01), and total scores (*p*=0.05). Conversely, a negative linear relationship was observed between the SDSC score and the ABAS GAC and ABAS CAD scores (*p*=0.025).

Conclusion: We detected an SD in 71.1% of our sample, with a positive relation between SD and internalizing and externalizing symptom levels, especially hyperactivity and impulsivity. Our study demonstrated a high prevalence of SD in pediatric patients with SoS, highlighting that all patients should be screened for this problem, which has a great impact on the quality of life of patients and their families.

1 Introduction

Sotos syndrome (SoS) is a rare overgrowth autosomal dominant syndrome with an incidence of approximately 1:14,000 live births [1]. It is determined by intragenic mutations or microdeletions of the *NSD1* gene (nuclear receptor set domain-containing protein 1) located on chromosome 5q35 [2]; in 95% of cases, it is caused by a *de novo* mutation [3]. Recent studies have demonstrated that *NSD1* is involved in the MAPK/ERK pathway, an important regulator of cellular proliferation, differentiation, and apoptosis [4]. The *NSD1* gene product is expressed in several organs, including the brain, skeletal muscle, white blood cells, lung, spleen, kidney, and thymus, and it has a role in the regulation of gene transcription.

The syndrome was described for the first time in 1964 by Juan Sotos [5], but diagnostic criteria (facial features, overgrowth, and developmental delay/learning disability) were defined only later in 1994 by Cole and Hughes [6]. Considering the features observed in 266 patients with mutations in the *NSD1* gene, major characteristics, cardinals, and associated features were identified (Table 1).

SoS population presents a heterogeneous neuropsychological profile, with possible cognitive impairment of various degrees and a spectrum of different neuropsychiatric manifestations, including autism spectrum disorder (ASD), hyperactivity [12–19], oppositive symptoms [20], separation anxiety [21], and self- and heteroaggressiveness [22]. A recent study conducted by our research team on 64 patients with SoS suggested that 5q35 microdeletion is associated with a higher severity of neuropsychiatric symptoms (including cognitive skills and behavioral issues) compared to mutation [23].

Patients with SoS also present impaired sleep habits. The first information about sleep disorders was reported in 1991 by Rutter [20], but only 30 years later this problem was further investigated [24], probably due to the rarity of the syndrome and the limited number of samples to be studied.

The present study aimed to assess the prevalence of sleep disorders in a cohort of children and adolescents with SoS and evaluate a possible relationship with the behavioral symptoms.

2 Materials and methods

The study involved patients who have been enrolled in the Child Neuropsychiatry Unit of Tor Vergata University Hospital of Rome. The population of this observational study is composed of SoS individuals included in a previous project conducted by our research team [23]. The inclusion criteria of the present study were: a genetic diagnosis of SoS; age up to 18 years; and the availability to complete our questionnaires. In the context of our previous study [23], SoS patients underwent a complete neuropsychological standardized assessment, including cognitive intelligent quotient (IQ) evaluation through the non-verbal Leiter-R (Leiter international performance scale-revised), adaptive functioning (ABAS-II – Adaptive Behavior Assessment System-Second Edition), and parent-report behavioral questionnaire (CBCL, child behavior checklist; CPRS-R:L; Conners' Parents Rating Scale-long form).

The Leiter-R is a standardized scale administered to children with communicational difficulties aged 2 to 20 years to evaluate their non-verbal cognitive abilities. The Leiter – R consists of 10 subtests:

TABLE 1 Clinical features of SoS.

Cardinal features >90%	• Overgrowth (height and occipitofrontal circumference ≥ 2 standard deviations above mean values) • Facial dysmorphisms like thin and elongated face, long chin, forehead prominent, dolichocephaly, sparse frontotemporal hair, and drooping palpebral fissure [7] • Variable intellectual disability [8]
Major characteristics 15–90%	• Behavioral problems • Hypotonia • Seizures • Joint hyperlaxity • Scoliosis • Genitourinary anomalies • Cardiac anomalies
Associated features <15%	• Neuroendocrine tumors • Hematological tumors • Cataract • Gastroesophageal reflux • Conductive hearing loss • Cryptorchidism • Hemihypertrophy [3, 8–11]

figure ground (FG), design analogies (DAs), form completion (FC), matching (M), sequential order (SO), repetitive pattern (RP), picture context (PC), classification (C), paper folding (PF), and figure rotation (FR), which make it possible to obtain a standardized non-verbal IQ score. In patients with more difficulties, it is possible to evaluate a brief IQ score through the FG, FC, So, and RP subtests [25].

The ABAS-II is a parent-report questionnaire available in two forms depending on the participant's age: "0–5" and "5–21." It provides information about the child's adaptive functioning through the 241 parents' answers for the "0–5″ form and 232 answers for the "5–21″ form, with scores ranging from 0 ("not able to") to 3 ("able to do it and always performs it when needed"). The answers provide a way to define four skill domains: social (SAD), conceptual (CAD), practical (PAD), and General Adaptive Composite (GAC) scores deriving from the sum of other skill domains [26].

The typical score in the Leiter-R and ABAS-II is 100 ± 15 standard deviation, while the significant score is lower than 85.

The Achenbach Child Behavior Checklist (CBCL) is a parent-report questionnaire administrable in two forms depending on the child's age: "18 months–5 years" and "6–18 years." The answers provided by the parents allow us to obtain scores regarding behavioral problems and emotional symptoms using scores from 0 (not true) to 2 (often true). Considering the "18 months–5 years" form, the following areas are possible to detect: anxious/depressed, aggressive behavior, sleep problems, withdrawal, attention problems, emotional reactions, and somatic complaints. In the "6–18 years" form: withdrawn/depressed, social problems, somatic complaints, thought problems, aggressive behavior, rule-breaking behavior, anxious/depressed, and attention problems. Both forms have internalizing, externalizing, and total scores that can be considered unique scores for the statistical analysis. Considering the T-score, a behavior is

considered borderline between 65 and 69, or significantly atypical, equal to or greater than 70 (27).

The Conners' Parent Rating Scale-Revised (CPRS-R:L) is a parent-report questionnaire able to detect externalizing behavior constituted by 80 items organized in seven subscales (oppositional, social problems, anxious-shy, hyperactivity-impulsivity, perfectionism, and psychosomatic cognitive problems) (28). Total Conners' Global Index (CGI), CGI Emotional Lability, CGI Restless-Impulsiveness, Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV Total, DSM-IV Inattention, DSM-IV Hyperactive–Impulsive, and attention deficit hyperactivity disorder (ADHD) index scores are further detectable subscales (29). The T-score ranging from 61 to 69 is considered borderline, while it is significant if it is equal to or greater than 70 (28).

Parents were also asked to fill out an online survey that investigated medical comorbidities, with a focus on epilepsy and allergies, pharmacological treatment (including all neurological drugs and antihistaminics), rehabilitation therapy, instrumental examinations, and previous diagnoses of sleep disturbances.

Sleep quality was investigated through a thorough clinical history and the Sleep Disturbance Scale for Children (SDSC).

SDSC is a questionnaire validated by Bruni et al. in 1996 as a screening tool for pediatric sleep disorders. The answers to the 26 questions are converted into scores ranging from 1 to 5 depending on the frequency of the disturbance: 1 for never, 2 for occasionally, 3 for sometimes, 4 for often, and 5 for always (30).

The six most frequent types of disorder in adolescence and childhood are investigated: disorders in the initiation and maintenance of sleep (DIMS), sleep breathing disorders (SBDs), disorders of arousal (DA), sleep–wake transition disorders (SWTDs), disorders of excessive sleepiness (DOES), and night-time sweating (hyperhidrosis, SHY). The questionnaire is suggestive of sleep disturbances if the total score is equal to or greater than 39 and equal to or greater than 17 in the DIMS subscale, 7 in the SBD and SHY areas, 6 in DA, 14 in SWTD, and 13 in DOES.

Data from the clinical assessment and online survey were matched and included in a unique database for statistical analysis.

Demographical features considered for the purpose of the study were sex, age, intellectual disability (ID), genetic microdeletion, history and active epilepsy, other non-neurologic comorbidities, antiseizure medication (ASM), other pharmacological treatments, and SD diagnosis.

An intellectual disability diagnosis was postulated considering the Leiter-R IQ score and the GAC score in the ABAS-II questionnaire.

The study protocol has been approved by the Ethical Committee of Tor Vergata University Hospital of Rome, Italy (#6022). All parents signed the informed consent form.

3 Results

The SDSC questionnaire was proposed to the parents of 64 SoS patients enrolled in our previous project (23), with a 60% response rate and therefore a total of 38 valid questionnaires. The mean age at completion was 11.1 ± 4.65 years. Male individuals were 60.5% ($n = 23$). The demographic and clinical characteristics of our sample are summarized in Table 2.

Microdeletion of the *NSD1* gene was detected in 31.6% ($n = 12$) of patients, while 63.2% ($n = 24$) presented an intragenic mutation. Genetic data were not available in 5.3% ($n = 2$).

Intellectual disability was diagnosed in 17 patients (44.7%). Ten patients had a history of epilepsy, of whom one had active epilepsy at the time of our evaluation (considering at least one seizure in the last year) and four were still on antiseizure medications. Among 12 individuals (31.6%), other non-neurologic medical conditions were present, with allergies ($n = 7$, 58.3%) being the most frequent one. Only two patients (5.3%) reported a previous diagnosis of sleep disorder.

3.1 Sleep disturbance scale for children

A score above the cutoff was found in 71.1% ($n = 27$), and the overall mean total score was 45.2 ± 12.3 (range 28–80).

As for the subscales, 6 (15.8%) patients in the DIMS scale, 10 (26.3%) in SBD, 4 (10.5%) in DA, 10 (26.3%) in SWTD, 2 (5.2%) in DOES, and 7 (18.4%) in SHY obtained a score above the cutoff (Supplementary Figure 1).

The mean reported sleep onset latency was 15 min, while the mean total sleep time was 8–9 h.

The chi-square test did not reveal a statistically significant association between a positive score in SDSC and genetic microdeletion ($p = 0.63$), sex ($p = 1$), ID ($p = 1$), epilepsy history ($p = 0.7$), active epilepsy ($p = 0.3$), ASM ($p = 1$), other drug intakes ($p = 1$), rehabilitation ($p = 0.4$), and other non-neurological comorbidities ($p = 0.4$).

3.2 Correlation of SDSC scores and behavioral symptoms

Twenty-nine patients (83%) achieved values above the cutoff in ABAS (mean score 68.6), 27 (84%) in CBCL (mean score 58.7), and 9

TABLE 2 Demographic and clinical characteristics of 38 participants.

	N	%
Total	38	
Mean Age	11.1 ± 4.65 years	
Female: Male	15:23	39: 61
Genetics (Microdeletion: Intramutation: Unavailable)	12: 24: 2	31.6: 63.2: 5.3
Epilepsy	10	26.3
Antiseizure medications	4	10.5
Other drugs	5	13.1
Other medical comorbidities	12	33
Allergies	7	58.3
Orthopedic	7	58.3
Genitourinary	2	16.6
Gastrointestinal	2	16.6
Eye	2	16.6
Cardiac	2	16.6
Orthodontic	1	8.3
Rehabilitation	28	73.7
Sleep disorder diagnosis	2	5.3
Sleep disorder treatment	2	5.3

(26%) in Conners (mean score 61.6). The scores for all the subscales are reported in Table 3.

The application of a two-tailed Student's t-test for independent samples revealed no significant differences in mean scores of Conners, CBCL, and ABAS between subjects with and without an SD (Table 4).

Linear regression reveals a positive relationship between the SDSC scores and Conners' and CBCL subscales regarding externalizing and internalizing symptoms (Conners' CGI Total and Conners' restless/impulsive, CBCL externalizing, internalizing, and total score). This indicates that an increase in these values is associated with an increased SDSC score. Furthermore, there is a negative linear relationship between the SDSC score and ABAS subscales.

In the logistic regression model including IQ, Conners', CBCL's, and ABAS's subscale independent variables, none of them appeared to be a significant risk factor for positive SDSC. All the statistical linear regression test scores and logistic regression model scores are reported in Table 5.

4 Discussion

In our sample, we were able to detect sleep disorders in 71.1% of patients through a comprehensive collection of detailed clinical histories and the administration of the SDSC. This finding demonstrates that these disorders are much more prevalent in children and adolescents with SoS than in the general pediatric population, where the prevalence is 20–30% (31–33).

The most commonly identified sleep problems were SBD and SWTD, both occurring in 26.3%, possibly linked to the high incidence of congenital malformations of the neck and head in this population, such as general hypotonia, including weakness in the muscles of swallowing, macroglossia, high arched palates, alveolar cleft and cleft lip, and palate, which could contribute to respiratory and feeding difficulties (34). Regarding the other subscales, we observed a score above the cutoff for SHY at 18.4% and for DIMS at 15.8%.

In our sample, SD is not significantly associated with genetic microdeletion, ID, or other medical conditions and treatments.

However, the SDSC score is related to the level of internalizing and externalizing symptoms, particularly in the hyperactivity and impulsivity domains. According to our findings, better adaptive functioning is correlated with lower SDSC scores. This is noteworthy despite all the adaptive functioning scores identified with ABAS-II being significantly pathological, indicating an adaptive functioning level below the normal range.

Behavioral problems within the SoS spectrum are among the major characteristics, with a prevalence ranging from 15 to 90%, depending on the examined study group. It is important to note that, being a rare syndrome, literature data often refer to case reports or small studies.

In 1991, Rutter first described sleep problems related to early awakenings in a small sample of 11 SoS subjects (20). In a recent study, 40 patients with a mean age of 11 years (1.3–30 years) and genetic, possible, and probable diagnoses of SoS were compared with data from healthy subjects in the literature. The study showed increased resistance at bedtime, anxiety surrounding sleep, nocturnal awakenings, parasomnias, daytime sleepiness, and evidence of sleep-disordered breathing (SDB). The authors compared their population with one presenting intellectual and developmental disabilities, and they found that patients with SoS more frequently presented SBDs and

parasomnias (24). These studies have certain limitations. Rutter (20) employed a non-standardized parent report. In the study conducted by Stafford et al. (24), participants with probable, possible, and genetically diagnosed SoS were included. They completed the Children's Sleep Habits Questionnaire (CHSQ), validated for children aged 4 to 10 years, to establish a standardized parameter for all included patients, regardless of age (1.3 to 30 years old).

Sleep issues are prevalent across all stages of childhood, encompassing infants, toddlers, preschoolers, school-age children, and adolescents. During children's brain development, sleep plays a key role, necessary for typical synaptic development and maturation of brain areas (35). Poor sleep can have significant repercussions on the cognitive side, and, due to the involvement of the prefrontal cortex, it can also lead to alterations in executive functions (36–38). It is also associated with behavioral disturbances, particularly a tendency toward externalizing disorders (39), irritability, and difficulty modulating emotions and impulses (39–41). Several studies have demonstrated the correlation between good sleep and a positive impact on future behavioral and socioemotional aspects lasting into adulthood (39, 42, 43). Chronic poor sleep habits, particularly short sleep durations, can also increase the risk of obesity and metabolic diseases (44–46). Sleep-related breathing disorders, ranging from habitual snoring to obstructive sleep apnea syndrome, can significantly affect emotional intelligence, cardiovascular functions, orofacial thrive, and the neuroendocrine and central nervous systems (47).

TABLE 3 Conners', CBCL, and ABAS scores.

	Mean score	Median score	SD	Range
Conn_Oppositional	57.29	56	13.109	38–100
Conn_Cognitive problems	68.5	70	13.765	44–99
Conn_Hyperactivity	63.18	60	15.353	42–96
Conn_Anxious/Shy	59.91	56.5	13.666	41–88
Conn_Perfectionistic	53.64	51	10.694	36–84
Conn_Social Problems	68.2	64	19.043	42–99
Conn_Psychosomatic	51.12	48	9.943	39–82
Conn_ADHD Index	68.45	69	14.107	41–99
Conn_Restless/Impulsive	63.27	65	12.471	37–89
Conn_Emotional Lability	55.28	50.5	14.195	39–91
Conn_Global Index	61.16	62.5	13.274	38–91
Conn_DSM_IV (Inattentive)	65.35	67	13.289	41–98
Conn_DSM_IV_(Hyperactive–Impulsive)	61.73	61	12.751	42–90
Conn_DSM_IV_(ADHD total symptoms)	65.12	66	13.239	41–100
CBCL Externalizing_1_18	56.9	56.5	9.918	40–80
CBCL Internalizing_1_18	59.47	61	13.061	34–100
CBCL Total_1_18	59.72	62.5	10.142	34–75
ABAS_GAC_PC	66.09	63	20.914	40–120
ABAS_CAD_PC	71.29	67	20.423	43–120
ABAS_SAD_PC	72.03	70	17.070	50–120
ABAS_PAD_PC	65.09	58	21.861	40–113

IQ, intelligent quotient; Conn, Conners; ADHD, attention-deficit hyperactivity disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; CBCL, Achenbach Child Behavior Checklist; ABAS, Adaptive Behavior Assessment System; GAC, General Adaptive Composite; CAD, conceptual domain; SAD, social domain; PAD, practical domain.

TABLE 4 Two-tailed Student's *t*-test for independent samples.

	SD	Mean	Mean Difference	Std. error difference	T	95% C.I.
IQ	0	83.29	9.202	11.369	p = 0.747	−14.050; 32.454
	1	74.08				
Conn_Oppositional	0	54.27	−4.394	4.784	p = 0.621	−14,128; 5.340
	1	58.67				
Conn_Cognitive problems	0	66.27	−3.292	5.091	p = 0.290	−13.663; 7.078
	1	69.57				
Conn_Hyperactivity	0	60.55	−3.955	5.716	p = 0.824	−15.613; 7.704
	1	64.50				
Conn_Anxious/Shy	0	60.73	1.206	5.083	p = 0.541	−9,148; 11,559
	1	59.52				
Conn_Perfectionistic	0	50.60	−4.357	4.041	p = 0.690	−12.597; 3.884
	1	54.96				
Conn_Social Problems	0	76.36	11.905	6.726	p = 0.409	−1.779; 25.589
	1	64.46				
Conn_Psychosomatic	0	50.00	−1.542	3.939	p = 0.848	−9.575; 6.492
	1	51.54				
Conn_ADHD Index	0	62.70	−8.257	5.223	p = 0.435	−18.908; 2.395
	1	70.96				
Conn_Restless/Impulsive	0	56.50	−9.717	4.471	p = 0.886	−18.835; −0.599
	1	66.22				
Conn_Emotional Lability	0	54.70	−0.845	5.501	p = 0.548	−12.080; 10.389
	1	55.55				
Conn_Global Index	0	55.30	−8.518	4.906	p = 0.393	−18.537; 1.500
	1	63.82				
Conn_DSM_IV (Inattentive)	0	62.73	−3.881	4.899	p = 0.754	−13,861; −6,098
	1	66.61				
Conn_DSM_IV_(Hyperactive–Impulsive)	0	59.18	−3.818	4.734	p = 0.781	−13.474; 5.838
	1	63.00				
Conn_DSM_IV_(ADHD total symptoms)	0	62.91	−3.265	4.894	p = 0.790	−13.234; 6.705
	1	66.17				
CBCL Internalizing_1_18	0	54.90	−6.645	4.916	p = 0.820	−16.685; 3.394
	1	61.55				
CBCL Externalizing_1_18	0	51.10	−8.400	3.526	p = 0.383	−15.601; −1.199
	1	59.50				
CBCL Total_1_18	0	55.60	−5.991	3.777	p = 0.702	−13.704; 1.722
	1	61.59				
ABAS_GAC_PC	0	71.55	7.962	7.604	p = 0.151	−7.508; 23.433
	1	63.58				
ABAS_CAD_PC	0	77.91	9.659	7.358	p = 0.259	−5.312; 24.630
	1	68.25				
ABAS_SAD_PC	0	72.91	1.284	6.305	p = 0.105	−11.543; 14.111
	1	71.63				
ABAS_PAD_PC	0	67.82	3.985	8.050	p = 0.171	−12.392; 20.362
	1	63.83				

IQ, intelligent quotient; Conn, Conners; ADHD, attention-deficit hyperactivity disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; CBCL, Achenbach Child Behavior Checklist; ABAS, Adaptive Behavior Assessment System; GAC, General Adaptive Composite; CAD, conceptual domain; SAD, social domain; PAD, practical domain.

Furthermore, studies have shown that caregivers of patients with sleep disturbances experience high levels of distress (48–50), and stress levels improve when the child's sleep habits improve (51, 52).

Therefore, early identification of an SD is crucial to prevent repercussions on the cognitive, emotional, and behavioral spheres, especially in a population that is genetically predisposed. It is essential to support families in managing this condition. Clinicians should

TABLE 5 Linear regression analysis and logistic regression model.

	Linear regression analysis			Logistic regression	
	Adj. R^2	Standardized coefficients	Sig.	Exp (B) odd ratio	Sig.
IQ	−0.032	0.049	$p = 0.794$	0.986	$p = 0.413$
Conn_Oppositional	0.020	0.220	$p = 0.204$	1.030	$p = 0.359$
Conn_Cognitive problems	0.000	0.173	$p = 0.328$	1.018	$p = 0.510$
Conn_Hyperactivity	0.003	0.185	$p = 0.303$	1.018	$p = 0.482$
Conn_Anxious/Shy	−0.026	−0.070	$p = 0.694$	0.993	$p = 0.807$
Conn_Perfectionistic	0.013	0.208	$p = 0.245$	1.045	$p = 0.284$
Conn_Social Problems	−0.029	−0.035	$p = 0.840$	0.966	$p = 0.091$
Conn_Psychosomatic	−0.024	0.091	$p = 0.615$	1.017	$p = 0.688$
Conn_ADHD Index	0.048	0.279	$p = 0.116$	1.047	$p = 0.129$
Conn_Restless/Impulsive	**0.146**	**0.415**	$\boldsymbol{p = 0.016}$	1.074	$p = 0.049$
Conn_Emotional Lability	−0.028	0.073	$p = 0.691$	1.004	$p = 0.874$
Conn_Global Index	**0.095**	**0.352**	$\boldsymbol{p = 0.048}$	1.057	$p = 0.100$
Conn_DSM_IV (Inattentive)	−0.001	0.172	$p = 0.329$	1.024	$p = 0.423$
Conn_DSM_IV_(Hyperactive–Impulsive)	0.002	0.183	$p = 0.307$	1.025	$p = 0.414$
Conn_DSM_IV_(ADHD total symptoms)	−0.001	0.173	$p = 0.329$	1.020	$p = 0.498$
CBCL Externalizing_1_18	**0.244**	**0.518**	$\boldsymbol{p = 0.02}$	1.118	$p = 0.037$
CBCL Internalizing_1_18	**0.274**	**0.546**	$\boldsymbol{p = 0.01}$	1.047	$p = 0.186$
CBCL Total_1_18	**0.207**	**0.483**	$\boldsymbol{p = 0.05}$	1.063	$p = 0.130$
ABAS_GAC_PC	**0.118**	**−0.379**	$\boldsymbol{p = 0.025}$	0.982	$p = 0.298$
ABAS_CAD_PC	**0.118**	**−0.379**	$\boldsymbol{p = 0.025}$	0.977	$p = 0.198$
ABAS_SAD_PC	0.069	−0.310	$p = 0.07$	0.996	$p = 0.834$
ABAS_PAD_PC	0.072	−0.315	$p = 0.07$	0.992	$p = s0.613$

IQ, intelligent quotient; Conn, Conners; ADHD, attention-deficit hyperactivity disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; CBCL, Achenbach Child Behavior Checklist; ABAS, Adaptive Behavior Assessment System; GAC, General Adaptive Composite; CAD, conceptual domain; SAD, social domain; PAD, practical domain.
For the linear regression analysis, the statistically significant scores are highlighted in bold font: Conn_Restless/Impulsive $p = 0.016$; Conn_Global Index $p = 0.048$; CBCL Externalizing_1_18 $p = 0.02$; CBCL Internalizing_1_18 $p = 0.01$; CBCL Total_1_18 $p = 0.05$; ABAS_GAC_PC $p = 0.025$; ABAS_CAD_PC $p = 0.025$.
The logistic regression model shows no statistical probability of having SD considering IQ, Conners', CBCL, and ABAS subscales.

specifically evaluate this aspect, as in our population, only two patients have already had a diagnosis of SD.

Our study does have some limitations. Not all patients responded to our questionnaires, and it is likely that parents of those with sleep disturbances were more likely to respond, potentially influencing the final rate of SD detected in our population. Moreover, a comprehensive physical examination of all study participants to correlate with the high prevalence of sleep disorders in SBD and SWTD areas was not feasible. Nonetheless, it is well established that the SoS phenotype encompasses head and neck malformations.

5 Conclusion

To the best of our knowledge, this is the first study attempting to correlate the presence of sleep disorders with behavioral symptoms in the pediatric SoS population. Internalizing and externalizing symptoms, especially in the hyperactivity and impulsivity domains, are directly related to more severe sleep symptoms, whereas typical adaptive behaviors are associated with milder sleep problems. Early detection of sleep disorders is crucial

for enabling prompt treatment, reducing the onset of internalizing and externalizing problems, and preventing adverse impacts on the quality of life for caregivers.

Additionally, addressing behavioral symptoms may positively impact sleep, given the bidirectional connection between the two.

The high prevalence of SD in our population underscores the need to include an investigation of sleep habits and quality in the clinical evaluations of these patients to identify and manage them correctly.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Ethical Committee of Tor Vergata University Hospital of Rome, Italy. The

studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

IF: Data curation, Formal analysis, Writing – original draft. RS: Investigation, Writing – review & editing. MS: Writing – review & editing. AR: Writing – review & editing. CG: Writing – review & editing. MV: Writing – review & editing. GC: Writing – review & editing. DC: Writing – review & editing. LM: Writing – review & editing. RM: Conceptualization, Data curation, Formal analysis, Supervision, Writing – original draft.

Funding

Acknowledgments

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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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1360055/full#supplementary-material

References

1. Tatton-Brown K, Rahman N. Clinical features of NSD1-positive Sotos syndrome. *Clin Dysmorphol*. (2004) 13:199–04. doi: 10.1097/00019605-200410000-00001

2. Kurotaki N, Harada N, Yoshiura K, Sugano S, Niikawa N, Matsumoto N. Molecular characterization of NSD1, a human homologue of the mouse Nsd1 gene. *Gene*. (2001) 279:197–04. doi: 10.1016/S0378-1119(01)00750-8

3. Tatton-Brown K, Cole TR, Rahman N. Sotos Syndrome. In: MP Adam, GM Mirzaa, RA Pagon, SE Wallace, LJ Bean and KW Gripp, et al., *Gene reviews*® Seattle (WA): University of Washington, Seattle (2004)

4. Kim EK, Choi EJ. Pathological roles of MAPK signaling pathways in human diseases. *Biochim Biophys Acta (BBA) - Mol Basis Dis*. (2010) 1802:396–05. doi: 10.1016/j.bbadis.2009.12.009

5. Sotos JF, Dodge PR, Muirhead D, Crawford JD, Talbot NB. Cerebral gigantism in childhood: a syndrome of excessively rapid growth with Acromegalic features and a nonprogressive neurologic disorder. *N Engl J Med*. (1964) 271:109–16. doi: 10.1056/NEJM196407162710301

6. Cole TR, Hughes HE. Sotos syndrome: a study of the diagnostic criteria and natural history. *J Med Genet*. (1994) 31:20–32. doi: 10.1136/jmg.31.1.20

7. Allanson JE, Cole TRP. Sotos syndrome: evolution of facial phenotype subjective and objective assessment. *Am J Med Genet*. (1996) 65:13–20. doi: 10.1002/(SICI)1096-8628(19961002)65:1<13::AID-AJMG2>3.0.CO;2-Z

8. Tatton-Brown K, Douglas J, Coleman K, Baujat G, Cole TRP, Das S, et al. Genotype-phenotype associations in Sotos syndrome: an analysis of 266 individuals with NSD1 aberrations. *Am J Hum Genet*. (2005) 77:193–04. doi: 10.1086/432082

9. Tatton-Brown K. Multiple mechanisms are implicated in the generation of 5q35 microdeletions in Sotos syndrome. *J Med Genet*. (2005) 42:307–13. doi: 10.1136/jmg.2004.027755

10. Edmondson A, Kalish J. Overgrowth syndromes. *J Pediatr Genet*. (2015) 4:136–43. doi: 10.1055/s-0035-1564440

11. Gracia Bouthelier R, Lapunzina P. Follow-up and risk of tumors in overgrowth syndromes. *J Pediatr Endocrinol Metab*. (2005) 18:1227–35. doi: 10.1515/JPEM.2005.18.S1.1227/html

12. Gajre M, Mhatre P, Vijaykumar R. Sotos syndrome with developmental co-ordination disorder; report of a case. *J Taibah Univ Med Sci*. (2014) 10:234–7. doi: 10.1016/j.jtumed.2014.05.007

13. Gosalakkal JA. Sotos syndrome (cerebral gigantism): a review of neurobehavioral, developmental and neurological manifestations. *Int Pediatr*. (2004) 19:147–51.

14. Mouridsen SE, Hansen MB. Neuropsychiatric aspects of Sotos syndrome. A review and two case illustrations. *Eur Child Adolesc Psychiatry*. (2002) 11:43–8. doi: 10.1007/s007870200007

15. Jellinek M, Trad PV, Schlefer E, Hertzig M, Kernberg PF. Treatment strategies for a case of concurrent pervasive developmental disorder and cerebral gigantism. *J Am Acad Child Adolesc Psychiatry*. (1991) 30:499–06. doi: 10.1097/00004583-199105000-00024

16. de Boer L, Röder I, Wit J. Psychosocial, cognitive, and motor functioning in patients with suspected Sotos syndrome: a comparison between patients with and without NSD1 gene alterations. *Dev Med Child Neurol*. (2006) 48:582–8. doi: 10.1017/S0012162206001228

17. Finegan JAK, Cole TRP, Kingwell E, Smith ML, Smith M, Sitarenios G. Language and behavior in children with Sotos syndrome. *J Am Acad Child Adolesc Psychiatry*. (1994) 33:1307–15. doi: 10.1097/00004583-199411000-00013

18. Mauceri L, Sorge G, Baieli S, Rizzo R, Pavone L, Coleman M. Aggressive behavior in patients with sotos syndrome. *Pediatr Neurol*. (2000) 22:64–7. doi: 10.1016/S0887-8994(99)00105-8

19. Varley CK, Crnic K. Emotional, behavioral, and cognitive status of children with cerebral gigantism. *J Dev Behav Pediatr JDBP*. (1984) 5:132–4.

20. Rutter SC, Cole TRP. Psychological characteristics of sotos syndrome. *Dev Med Child Neurol*. (1991) 33:898–02. doi: 10.1111/j.1469-8749.1991.tb14799.x

21. Sarimski K. Behavioural and emotional characteristics in children with Sotos syndrome and learning disabilities. *Dev Med Child Neurol*. (2003) 45:172–8.

22. Sheth K, Moss J, Hyland S, Stinton C, Cole T, Oliver C. The behavioral characteristics of Sotos syndrome. *Am J Med Genet A*. (2015) 167:2945–56. doi: 10.1002/ajmg.a.37373

23. Siracusano M, Riccioni A, Frattale I, Arturi L, Dante C, Galasso C, et al. Cognitive, adaptive and behavioral profile in Sotos syndrome children with 5q35 microdeletion or intragenic variants. *Am J Med Genet A*. (2023) 191:1836–48. doi: 10.1002/ajmg.a.63211

24. Stafford CF, Ward C, Ward SLD, Sanchez-Lara PA. Characterization of sleep habits of children with Sotos syndrome. *Am J Med Genet A*. (2021) 185:2815–20. doi: 10.1002/ajmg.a.62212

25. Roid GH, Miller LJ. *Leiter international performance scale-revised: examiner's manual.* Roid G H and Miller L. J (Eds.), (1997). Stoelting.

26. Oakland T. *Adaptive behavior assessment system.* Kreutzer J. S, de Luca J, and Caplan B (Eds.), (2011). (2nd ed.) Springer.

27. Achenbach TM, Rescorla LA. *Manual for the ASEBA preschool forms & profiles.* (2000). University of Vermont.

28. Conners CK, Sitarenios G, Parker JDA, Epstein JN. The revised Conners' parent rating scale (CPRS-R): factor structure, reliability, and criterion validity. *J Abnorm Child Psychol*. (1998) 26:257–68. doi: 10.1023/A:1022602400621

29. Gurley JR. Conners' parent rating scales – revised In: S Goldstein and JA Naglieri, editors. *Encyclopedia of child behavior and development*. Boston, MA: Springer US (2011)

30. Bruni O, Ottaviano S, Guidetti V, Romoli M, Innocenzi M, Cortesi F, et al. The sleep disturbance scale for children (SDSC) construct ion and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. *J Sleep Res*. (1996) 5:251–61. doi: 10.1111/j.1365-2869.1996.00251.x

31. Mindell JA, Kuhn B, Lewin DS, Meltzer LJ, Sadeh AAmerican Academy of Sleep Medicine. Behavioral treatment of bedtime problems and night wakings in infants and young children. *Sleep*. (2006) 29:1263–76.

32. Staples AD, Bates JE, Petersen IT. Ix. Bedtime routines in early childhood: prevalence, consistency, and associations with NIGHTTIME sleep: bedtime routines. *Monogr Soc Res Child Dev*. (2015) 80:141–59. doi: 10.1111/mono.12149

33. Turnbull K, Reid GJ, Morton JB. Behavioral sleep problems and their potential impact on developing executive function in children. *Sleep*. (2013) 36:1077–84. doi: 10.5665/sleep.2814

34. Danis DO, Bodamer O, Levi JR. The otolaryngologic manifestations of Sotos syndrome 1: a systematic review. *Int J Pediatr Otorhinolaryngol*. (2021) 143:110649. doi: 10.1016/j.ijporl.2021.110649

35. Hirata I, Mohri I, Kato-Nishimura K, Tachibana M, Kuwada A, Kagitani-Shimono K, et al. Sleep problems are more frequent and associated with problematic behaviors in preschoolers with autism spectrum disorder. *Res Dev Disabil*. (2016) 49-50:86–99. doi: 10.1016/j.ridd.2015.11.002

36. Bernier A, Beauchamp MH, Bouvette-Turcot AA, Carlson SM, Carrier J. Sleep and cognition in preschool years: specific links to executive functioning. *Child Dev*. (2013) 84:1542–53. doi: 10.1111/cdev.12063

37. Nelson TD, Nelson JM, Kidwell KM, James TD, Espy KA. Preschool sleep problems and differential associations with specific aspects of executive control in early elementary school. *Dev Neuropsychol*. (2015) 40:167–80. doi: 10.1080/87565641.2015.1020946

38. Sadeh A. Consequences of sleep loss or sleep disruption in children. *Sleep Med Clin*. (2007) 2:513–20. doi: 10.1016/j.jsmc.2007.05.012

39. Touchette É, Petit D, Séguin JR, Boivin M, Tremblay RE, Montplaisir JY. Associations between sleep duration patterns and behavioral/cognitive functioning at school entry. *Sleep*. (2007) 30:1213–9. doi: 10.1093/sleep/30.9.1213

40. Ednick M, Cohen AP, McPhail GL, Beebe D, Simakajornboon N, Amin RS. A review of the effects of sleep during the first year of life on cognitive, psychomotor, and temperament development. *Sleep*. (2009) 32:1449–58. doi: 10.1093/sleep/32.11.1449

41. Scharf RJ, Demmer RT, Silver EJ, Stein REK. Nighttime sleep duration and externalizing behaviors of preschool children. *J Dev Behav Pediatr*. (2013) 34:384–91. doi: 10.1097/DBP.0b013e31829a7a0d

42. Hale L, Berger LM, LeBourgeois MK, Brooks-Gunn J. A longitudinal study of preschoolers' language-based bedtime routines, sleep duration, and well-being. *J Fam Psychol*. (2011) 25:423–33. doi: 10.1037/a0023564

43. Wong MM, Brower KJ, Zucker RA. Childhood sleep problems, early onset of substance use and behavioral problems in adolescence. *Sleep Med*. (2009) 10:787–96. doi: 10.1016/j.sleep.2008.06.015

44. Knutson KL. Does inadequate sleep play a role in vulnerability to obesity? *Am J Hum Biol*. (2012) 24:361–71. doi: 10.1002/ajhb.22219

45. Leproult R, Van Cauter E. Role of sleep and sleep loss in hormonal release and metabolism In: S Loche, M Cappa, L Ghizzoni, M Maghnie and MO Savage, editors. *Endocrine Development* (2010) 17:11–21. doi: 10.1159/000262524

46. Miller MA, Kruisbrink M, Wallace J, Ji C, Cappuccio FP. Sleep duration and incidence of obesity in infants, children, and adolescents: a systematic review and meta-analysis of prospective studies. *Sleep*. (2018) 41. doi: 10.1093/sleep/zsy018/4833233

47. Operto FF, Precenzano F, Bitetti I, Lanzara V, Fontana ML, Pastorino GMG, et al. Emotional intelligence in children with severe sleep-related breathing disorders. *Behav Neurol*. (2019) 2019:1–6. doi: 10.1155/2019/6530539

48. Schlieber M, Han J. The role of sleep in young Children's development: a review. *J Genet Psychol*. (2021) 182:205–17. doi: 10.1080/00221325.2021.1908218

49. Hiscock H, Wake M. Infant sleep problems and postnatal depression: a community-based study. *Pediatrics*. (2001) 107:1317–22. doi: 10.1542/peds.107.6.1317

50. Meltzer LJ, Mindell JA. Relationship between child sleep disturbances and maternal sleep, mood, and parenting stress: a pilot study. *J Fam Psychol*. (2007) 21:67–73. doi: 10.1037/0893-3200.21.1.67

51. Hiscock H, Bayer J, Gold L, Hampton A, Ukoumunne OC, Wake M. Improving infant sleep and maternal mental health: a cluster randomised trial. *Arch Dis Child*. (2007) 92:952–8. doi: 10.1136/adc.2006.099812

52. Mindell JA, Telofski LS, Wiegand B, Kurtz ES. A nightly bedtime routine: impact on sleep in young children and maternal mood. *Sleep*. (2009) 32:599–06. doi: 10.1093/sleep/32.5.599