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Sleep measurement and monitoring in children with Down syndrome: A review of the literature, 1960–2010

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SUMMARY

Children with Down syndrome (DS) are at risk for sleep disturbances due to the anatomical features of the syndrome. Over the past 50 years research studies have measured sleep in children with DS to characterize sleep architecture and its relation to developmental delay. In the 1980s sleep disordered breathing (SDB) was recognized as a major cause of sleep disturbance in DS. The aim of this comprehensive review is to synthesize studies and present the historical context of evolving technologies, methodologies, and knowledge about SDB and DS. Future research opportunities and practice implications are discussed.

Keywords

Down syndrome; Children; Sleep; Narrative review; Obstructive sleep apnea; Historical context

Objective

Published accounts of sleep research in Down syndrome (DS) have appeared in the literature since the 1960s. The purpose and methodologies of the studies have been diverse, each contributing differently to the current state of the science on sleep in DS. To our knowledge, a comprehensive synthesis of research findings about sleep and its characteristics in children with DS has not been published. The goal of this manuscript is to critically review and synthesize the history, methodologies, and findings from studies conducted in children with DS from the 1960s to 2010. A brief epidemiologic review of DS and its related clinical characteristics, a historical timeline of identification of DS, general technological developments in sleep measurement, and recognition of sleep disordered breathing (SDB) provides context for the reviewed studies.

Introduction

Epidemiology of Down syndrome

Approximately 5400 of the four million infants born in the United States (US) each year have DS. In recent years the rate of live births with DS has increased in the US, from ~1 in 1100 in 1979 to ~1 in 850 in 2003.¹ The prevalence of DS varies between 1/650 and 1/1000 worldwide.²⁻⁴ DS is the most common genetic cause of significant intellectual disability.⁵ DS affects the entire human population equally and is not dependent on geography, race, ethnicity, or socioeconomic standing.³ The prevalence of DS varies due to the interplay of a number of factors including changing trends in average maternal age, personal and religious views about intentional pregnancy terminations, as well as health care policy and national legislation leading to improved maternal health and prenatal care.⁶ Environmental factors such as smoking, alcohol consumption, fertility drugs, and contraceptives have not been shown to be significantly associated with increased risk of DS.⁴ Increased maternal age is the only known risk factor associated with DS, yet most children with DS are born to younger women because of higher general birth rates in this group.²

In early childhood, children with DS generally have delayed development of speech and fine and gross motor skills. In the developed world, early intervention programs address the needs of children with DS and other types of developmental delay (DD) with relatively good success.⁷ Because of life-saving advances in health care, such as pediatric cardiac surgery and improved societal accommodations, children with DS are living longer and healthier lives.^{2,8} In the first half of the 20th century, life expectancy was the early teenage years, and children were often institutionalized. Currently average life expectancy is close to 60 years; and in the developed world, almost all children with DS live in the community in a home environment.⁹ Thus, it has become increasingly important to optimize the health of children with DS through preventive measures to avoid secondary complications and set the stage for a healthier adulthood. This review will provide background information for researchers interested in improving the sleep of children with DS as one avenue for improved overall health.

Clinical characteristics of DS and relation to sleep

The phenotypic characteristics of DS include DD, short stature, flat nasal bridge and oblique eye fissures. These characteristics were first described by John Langdon Down in 1866,¹⁰ after whom the syndrome is named. In 1959, the etiology of DS was found to be an extra copy of chromosome 21¹¹⁻¹³; thus DS is also referred to as Trisomy 21. Chromosome 21 is one of the most studied human chromosomes. It has been fully sequenced,⁵ yet the functions of many genes on the chromosome remain unknown, and the mechanisms by which the trisomy leads to the phenotypes of DS are unclear.¹⁴ DS are typically diagnosed prenatally or at birth.

There are several clinical features of DS that potentially lead to disturbed sleep and/or increased risk for SDB. However, not all of these clinical characteristics are present in every child, and when present, vary in intensity. Hypotonia, relative macroglossia stemming from a normal size tongue not having enough room within a smaller size pharynx because of maxillary hypoplasia,¹⁵ small upper airway and underdeveloped midface (midfacial hypoplasia) are some of the physical features that may interfere with breathing during sleep and increase the risk of SDB.¹⁶ Additional SDB-predisposing characteristics in DS include crowding of the pharynx by a posteriorly-placed tongue, lymphoid hyperplasia (increased amount of tissue), reduction in pharyngeal muscle tone, and overweight.¹⁷ Children with DS are also at increased risk for congenital heart disease, pulmonary hypertension, leukemia, ear infections and scoliosis,⁶ all comorbidities potentially associated with disrupted sleep. In

light of the increased risk for SDB in DS, and the importance of nocturnal sleep in cognitive development, behavior and daytime function^{18,19} it is important to understand sleep architecture and the nature of sleep problems in children with DS in order to design preventative or supportive interventions to maximize the benefits of sleep in the population. This review synthesizes the work completed up to 2010 in pediatric DS sleep research.

Methods

Style and selection criteria of review

This review employs an inclusive methodology and narrative style to comprehensively examine previous accomplishments of sleep research in children with DS. As such it differs from a traditional quantitative systematic review which would focus on a well-defined question, narrowly focused on selective research with conforming measures. Because previous sleep research in children with DS asked diverse questions, implemented a variety of methodologies and standardized sleep monitoring and scoring standards were not used consistently,^{20,21} there are few studies appropriate for a quantitative systematic review.

The key words “Down syndrome,” “Down’s syndrome,” “Trisomy 21,” “Mongolism,” “Mongloid,” [DS was previously referred to as “Mongolism” through the 1970s] each in combination with “sleep,” were used in searches of PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library, Academic Search Complete, and Education Resources Information Center (ERIC). The searches were limited to articles published in English and in human subjects. Studies that included adults or mixed age groups of adults and children,^{22–25} daytime polysomnography and no nocturnal sleep measures^{26,27} were excluded. Single case reviews, editorials, and letters were reviewed for context. Twenty-six studies of nocturnal sleep in children with DS, ages 0–21 years, were found and included in this review. Twenty-three of the studies included overnight polysomnography (PSG) and were summarized in tabular format by chronological order, Table 1.^{28–49} The three remaining studies were parent-reports.^{50–52}

Categories of studies and chronological order

Studies of sleep in DS are categorized as: 1) basic research describing sleep, 2) applied research of sleep in association with medical problems, and 3) holistic research with an ecological view of health, including the social and medical context of comorbidities associated with sleep problems. A majority of the studies in this review fall into at least two of these categories. Most applied and holistic studies in DS sleep research involve obstructive sleep apnea (OSA), a general group of disorders further grouped under a category referred to as SDB. Although there is overlap in categories of studies, there is a temporal sequence in that typically basic research precedes applied research which is followed by holistic research. During the 20th century technological advancements and new scientific knowledge paved the way for advanced basic research and applied research aimed at improving medical outcomes in children with DS. A summary of this historical context of sleep research in relationship with DS is presented in Fig. 1.

Findings

Basic research – measurement of sleep architecture in relation to intellectual disability

The first studies of sleep in DS described normal and abnormal sleep architecture. In basic research, DS presented a homogeneous group with respect to etiology of DD, with well-defined physical characteristics and was considered representative of DD.^{28,29,31,34} Studies reported 3 to 5 sleep cycles alternating between non-rapid-eye movement (NREM) sleep and rapid eye movement (REM) sleep. REM sleep had been discovered in the early 1950s, and

since the 1960s a link had been observed between REM density and learning and mental function and disorders^{53,54}; thus REM sleep was a new and intriguing topic of study. The relation between sleep and learning has long been of scientific interest. In particular, studies in the 1960s and 1970s found associations between the amount of REM sleep and memory processing.^{55,56} Investigators were interested in discovering whether conditions associated with DD might be associated with a reduced amount or a lack of REM sleep. The first US polysomnographic study of children with DS compared the amount of REM sleep time between a group of boys with severe ($n = 5$) and moderate ($n = 5$) DD.²⁸ The average amount of REM sleep over 3 study nights was 59 min in the “severe” DD group compared to 93 min in the “moderate” DD group. A Japanese study compared differences in total sleep time (TST), percentage of time in each sleep stage, REM density, and number of stage shifts, night awakenings, and body movements among children with DS ($n = 10$), children with other types of developmental delay (OTDD) ($n = 10$), and typically developing (TD) children ($n = 8$).²⁹ TST, percentage of time in each sleep stage, number of stage shifts, night awakenings and body movements did not differ among the groups. However, DD severity was associated with lower REM density (11.5% vs. 8.5% in more severe DD, measured by IQ). The average number of stage shifts per minute was 0.08 ± 0.02 and the number of night awakenings was 2 ± 2 in DS which was comparable to both TD and OTDD, (0.1 ± 0.03 and 5 ± 4 , respectively). The REM amount of TST was $17 \pm 4\%$ for DS, $16 \pm 6\%$ for OTDD, and $20 \pm 7\%$ for TD. The proportion of TST designated as “indetermined sleep,” was $4 \pm 4\%$ in DS, $2 \pm 3\%$ in OTDD, and $1 \pm 2\%$ in TD.

Several studies examined the effects of pharmacological agents on sleep and daytime function in DS.^{30–32,57} Petre-Quadens and de Greef⁵⁷ and Petre-Quadens and de Lee³⁰ reported on the effects of 5-hydroxytryptophan (5-HTP) on “quiet” (non-REM) and “paradoxical” (REM) sleep in children with DS. Based on earlier findings by Bazelon et al.⁵⁸ who observed improvements in hypotonia, 5-HTP was administered to children with DS in a quasi-experimental study. Authors observed REM sleep density increases comparable to TD children, however noted this was a temporary effect and did not influence later development.³⁰ Grubar et al. and Gigli et al.^{31,32} examined the effect of butoctamide hydrogen succinate (BAHS) in children with DS. Based on Jackson’s 1932 theory on the relations between cognitive deficits and sleep, these two studies used BAHS, a type of hypnotic drug, to increase the minutes of REM sleep in children with DS. In addition to BAHS, two 6-hour [undescribed] intensive didactic sessions (IDS) were administered as an intervention to increase REM sleep.³² Neither intervention increased the percent time of REM sleep. However, TST was significantly lower in the intervention with IDS (532 min vs. 564 min, $p = <0.05$).

Basic sleep research continued through the 1980s to 2000s, and measures of arousal in various DD phenotypes (e.g., DS, fragile X syndrome) in relation to learning and memory were examined.^{34,36,45,46} Miano et al.⁴⁵ examined NREM cyclic alternating patterns in association with learning in DS ($n = 9$), fragile X syndrome (FXS) ($n = 14$), and age-matched TD controls. Those with DS had lower sleep efficiency, higher percentage of wake after sleep onset (WASO), and reduced percentage of stage 2 NREM sleep compared to the other groups. Compared to TD, children with DS and FXS showed a lower percentage of A1 and higher percentages of A2 and A3 stages.

Applied research – measurement of obstructive sleep apnea and its prevalence

Between 1980 and 1982, several editorials addressed the predisposition of children with DS to OSA because of physical features that place children at risk for airway obstruction during sleep.^{59–62} It was proposed that the onset of OSA may not be in early infancy, but rather arise later with the development of lymphoid hyperplasia between one and four years of age. Several PSG studies that examined OSA in DS clinical populations,^{33,39,43,44,47,49,63}

referred for snoring, sleep concerns, or other health problems reported a higher prevalence of OSA, ranging from 54% to over 90% compared to 1–4% of the typically developing and otherwise healthy children.¹⁹ By the time OSA was recognized as a concern in DS, methodologies to measure PSG-derived OSA were established with standard PSG monitoring. Electrocardiograms (ECG) and oximetry were integral to PSG; however many of the studies were retrospective case reviews, and the measurement methodologies varied by clinic and/or hospital. Although most studies defined OSA based on apnea-hypopnea index (AHI), definition of AHI differed across studies. For example, a respiratory event could be defined as absent or reduced airflow of “at least 5 seconds”,³⁸ “over 2 breath cycles”,^{47,49} or as “2 per hour or >3 per hour of TST”.^{39,40} Although AHI measurements may seem similar, the prevalence rates within the clinical studies varied due to differences in AHI definitions. Recently the AASM has reached consensus in defining AHI in pediatric populations.^{20,21}

Studies of OSA in DS using non-clinical community samples report prevalence rates between 24% and 59%.^{35,38,42} Although each of these groups used different thresholds for defining OSA, the two community samples with higher level of participation (see table), Dahlqvist et al. and Stebbens et al., showed lower prevalence of OSA, compared to studies with referred samples.^{33,39,43,44,47,49,63}

Applied research – clinic-based research studies that evaluated treatment of OSA

A few studies have examined the effects of surgical interventions and the use of continuous positive airway pressure (CPAP) for OSA in DS. There exist no clinical trials evaluating these interventions for sleep improvement in DS. Two retrospective case reviews focused on measuring sleep before and after surgical intervention, CPAP, or position therapy intervention for correction of OSA.^{47,48} Both studies documented improvements in OSA as a result of varied treatments. Rosen and colleagues reported spontaneous resolution of OSA in 3 of 6 infants with DS after several months of using CPAP, indicating that OSA in infants with DS can be a transient phenomenon.⁴⁶ Shete and colleagues reported improvements in sleep efficiency and AHI in children with and without DS who underwent adenotonsillectomy, although children without DS had greater improvements. Children with DS had pre-operative AHI and REM-AHI of 15 and 31, which decreased to 9 and 22 postoperatively. Pre-surgery, children without DS had AHI and REMAHI of 21 and 33 respectively, which were lowered to 2 and 6 post-operatively. Of note, 60% of children with DS had various comorbidities such as congenital heart disease and lung disease which affect breathing regardless of adenotonsillectomy. Among children with DS 73% needed additional intervention, such as CPAP, after surgery.

Holistic research – studies that look at the overall health and comorbidities

A few studies examined a broad holistic view of sleep problems in children with DS.^{46–49} Comorbidities such as congenital heart disease, pulmonary hypertension, and obesity in children with DS present challenges in treating sleep problems and disorders. O’Driscoll et al. reported reduced cardiovascular and ventilator responses exacerbate acute hypoxic exposure in DS.⁴⁶ Much of what is known about obesity and OSA stem from studies in TD children. Two studies examined obesity in relation to OSA in children with DS, with inconsistent findings. Fitzgerald and colleagues found no association between body mass index (BMI) and OSA in children with DS who snored.⁴⁴ The study found 9% of participants met the criteria for obesity based on DS-specific weight for height charts. Shires et al. conducted a retrospective case review of 52 children with DS who had PSG, and found an association between OSA and increased BMI, which increased with age.⁴⁹

Parent report studies

In three questionnaire studies parents reported on symptoms suggestive of sleep disorders. Carter et al. conducted a community prevalence study of sleep problems in DS using the child sleep habits questionnaire,⁵¹ and found that compared to parents of TD children, parents of children with DS reported more bedtime resistance (25%), not falling asleep in own bed (33%), restlessness during sleep (58%), night wakings (40%), daytime tiredness (70%), and bedwetting (26%). Cotton and Richdale⁵⁰ examined parental perceptions of the night time sleep in children with DS, autism, PraderWilli syndrome (PWS) and TD children. Children with DS had more sleep problems than TD children, but fewer sleep problems than those with autism or PWS. Another study conducted in the same year, 2006, measured sleep by both parent report and PSG, reported a discrepancy between parent reports and PSG results in children with DS. Of children who had abnormal PSGs only 34% had corresponding parent report of sleep problems.⁴³ A recent parent report study by Rosen et al.,⁵² using an anonymous internet survey of a clinical population, found that 47% of parents reported witnessed apneas following adenotonsillectomy, underscoring the need for continued monitoring for OSA after surgical intervention.

Discussion

In examining sleep in children with DS, it is important to consider the measurement of sleep in the context of advancing technology, varying research methodologies and research ethics, changing attitudes about DS, and different cultural and geographic settings. Some of the research studies in this review, though probably conforming to the standards of the day, would not be acceptable in today's regulatory and ethical environment.

Often early studies did not specify recruitment methods and were performed on institutionalized individuals likely without written consent of parents. In the 1960s and 1970s, research on institutionalized and/or those with DD, was not regulated as it is currently, after the 1979 Belmont report.⁷⁸ The 1970s and 1980s saw an increase in de-institutionalization in the developed world⁹ as more parents opted to raise their children with DS at home. In the 1980s studies included institutionalized subjects,^{31,32} however parent consent was mentioned explicitly in some studies during the late 1980s and early 1990s.^{32,35} Gigli et al. described for the first time the environment of the laboratory as a quiet, partially soundproofed, shielded laboratory within the institution, where children came with familiar assistants who stayed with them until they fell asleep.

In 1987, Southall and colleagues published the first study that evaluated OSA with PSG in children with DS.³³ Though considered a landmark study, like most early studies, the sample was small and biased due to pulmonary vascular disease present in the children. Most studies used clinical populations with comorbidities that are challenging to interpret due to confounding factors. Furthermore, in most studies, the number of subjects was inadequate for statistical evaluation and generalizability was limited. PSG is a costly and inconvenient method regardless of the presence of DS. Therefore PSG studies typically do not have a large number of participants. Nevertheless, these studies provide valuable information to build upon.

The measurement of sleep in children with DS evolved through advancing technology and consensus on sleep measurement. Early studies focused more on understanding sleep patterns in a homogeneous population with intellectual disability. Later studies sought to measure the prevalence of sleep problems and disorders and ways to resolve them. Only in recent years has the importance of chronologic age to sleep patterning received attention,¹⁹ thus some early studies tended to lump wide age groups of children with DS into single studies. Indeed a widely-cited DS pediatric sleep study included an age-range of 050

years.²⁴ This study was excluded from the current review because it was impossible to articulate the pediatric implications. As the field of pediatric sleep becomes more refined it is imperative for future research measuring sleep in DS to use standardized methods such as those described by Accardo et al. and Grigg-Damberger et al.^{20,21} For example, authors need to specify the environment of measurement and whether a parent accompanied the child. Such descriptions were absent from a majority of the papers reviewed in this report.

Most studies did not specify a classification of OSA as mild, moderate or severe, and results were based on the average of a wide range of characteristics. The presence or absence of OSA was measured using different standards among these studies. Studies that evaluate the effectiveness of surgical interventions would benefit from a standard diagnosis and severity measurement.^{41,47,48} It is important to know whether an intervention at least partially resolves OSA, rather than only complete resolution. Furthermore, the confounders of ear and upper respiratory infections, tonsils presence/size, heart and lung issues, hypertension, and other factors known to affect sleep or breathing during sleep, need proper assessment and reporting within studies.

Few studies have addressed the role of obesity in DS and its association with sleep problems.⁴² One study that found no association between obesity and OSA used a clinical population, 91% of whom were not considered obese based on DS growth charts.⁴⁴ DS-specific charts classify a smaller proportion of children as obese compared to Center for Disease Control (CDC) growth charts for TD children (<http://www.cdc.gov/growthcharts/>). It is unknown what proportion would have been considered obese based on these CDC growth charts. In contrast, another study used both DS and normal growth charts and found an association between obesity and OSA in DS, using either of the standards.⁴⁹

Given the morphological features of DS that are conducive to OSA, it seems important to consider using obesity standards based on TD growth charts. Why not hold children with DS to the same standards for obesity as the general population of children especially given our current awareness of obesity association with poor sleep and related unhealthy outcomes? As the population of children with DS is expected to live decades longer than previous generations, it is important to raise the expectations of adequate sleep and overall health outcomes as with any other population of children. It is important to teach healthy sleep, activity, and eating habits at an early age so that these habits and behaviors can become health promoting routines carried into adulthood. Early healthy sleep habits and routines are critical for all children, but may be even more critical in children with DS due to the underlying disease mechanisms and comorbidities. Modifiable environmental factors, such as exposure to tobacco smoke, also need to be considered as part of a comprehensive preventive plan.⁶⁵

In prevalence studies (e.g.,^{34,37,41}) information about family response rates would be useful to interpret generalizability and address future recruitment issues in communities. Potential reasons for low response could be perception of no sleep problems as reported by Shott et al.⁴³; perception that if there is a problem there would not be an easy solution because the child would refuse the most common treatment of CPAP; unwillingness of parents to put the child through a night of laboratory measurement; or, in a child with prior tonsillectomy, the parent may believe the sleep problem has been resolved to the extent possible.

Few studies highlight the importance of universal and frequent assessment of sleep problems in children with DS, not only for diagnosis but also for assessing improvement with or without treatment.^{43,47} One study discussed the potential negative unintended consequences of treatment such as the concern of worsening midface hypoplasia secondary to wearing a

CPAP interface for longer than necessary. These issues seem essential to promoting improvements in sleep of children with DS.

Conclusions

Recent studies emphasize the importance of childhood determinants of health in adulthood.⁶⁴ Because of the longer life expectancy in children with DS, it is important to maximize comprehensive health in their childhood to build a foundation for their adult health. Optimal sleep is essential for health, yet studies to date consistently report sleep concerns in children with DS. Many studies lack a theoretical framework to explain the overall picture of sleep problems in children with DS. Prior studies have used clinical populations likely to experience sleep problems. Some have treated subjects as individual cases, reporting individual outcomes, and have used varying methodologies. More systematic research on sleep problems and intervention in children with DS is warranted.

Limitations of this review

This review included only English language literature up to December 2010. The type of PSG equipment was not a consideration in this narrative review because although some authors reported their equipment specifications many did not, and when addressed it varied from study to study. Calibration of equipment was not discussed in this review because it was rarely addressed in the publications, yet it is well known that calibration problems can introduce bias in measurements.

Practice points

1. The patterning of sleep in children with DS has interested researchers for years because of the perceived relation of sleep with intellectual ability.
2. Characterizing and understanding the nature of sleep problems in children with DS is an essential element in prevention of secondary conditions in children with DS. Children with DS have a longer life expectancy than in the past; it is important to maximize health.
3. Sleep disordered breathing, specifically OSA, is recognized as a major sleep problem in children with DS. Assessing the size of tonsils has a major role in addressing this problem. Tonsillectomy resolves 30–50% of OSA in DS.
4. Practitioners are advised to screen for sleep disorders in children with DS despite a lack of history of snoring. Regular sleep assessments after tonsil/adenoid surgery are recommended.

Research agenda

1. Assess the reliability of diagnostic monitoring such as overnight oxygen monitoring, or actigraphy in child's home.
2. Incorporate actigraphy for assessment of sleep, and other home measures, over days, in all age groups, compare child and family patterns.
3. Measure the overall environment of the child to assess sleep problems. Consider home environment, the role of TV, lights, noise in the house and neighborhood, etc.
4. Trial sleep position therapy for OSA.

5. Trial early intervention to determine if it improves outcomes. For example, would early preschool CPAP use increase child acceptance?
6. Complete longitudinal studies to depict the history of sleep apnea in DS with treatment. How does it change as the person grows?
7. Basic research in REM sleep of children with DS who do not have OSA. This is important since most early studies did not specify OSA as a consideration and OSA was a confounder in later studies.
8. Surgery corrects 30-50% of cases of sleep apnea in DS, but what about severity levels? Does it reduce severity in cases not completely resolved? Conduct systematic studies to assess severity before and after various treatments.
9. Include qualitative studies and future quantitative studies about attitudes of parents toward sleep and obesity—should children with DS be held up to normal standards of obesity?
10. Incorporate Tanner staging, hormone levels, and circadian rhythms in studies of relation of sleep problems to obesity in DS.
11. Examine the extent to which the severity of OSA can be reduced by just reducing obesity.
12. Conduct studies to determine the role passive smoking plays in associations between DS and OSA.
13. Conduct genetic studies – understanding chromosome 21 genes and why some are protective and some promote illness?
14. In light of the importance of chronologic age to sleep patterning in children, using narrow age groups may help characterize sleep problems more specifically in children with DS.
15. Many research studies in the past did not specify consent circumstances, nor did they describe the laboratory conditions. These circumstances need to be clearly stated in future research.

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Abbreviations

5-HTP	5-hydroxytryptophan
AASM	American Academy of Sleep Medicine
AHI	apnea/hypopnea index
BAHS	butoctamide hydrogen succinate
BMI	body mass index
CDC	Center for Disease Control

CPAP	continuous positive airway pressure
DD	developmental delay
DS	Down syndrome
ECG	electrocardiogram
FXS	fragile X syndrome
IDS	intensive didactic sessions
NREM	non-rapid eye movement
OTDD	other types of developmental delay
PSG	polysomnography
PWS	Prader-Willi syndrome
REM	rapid eye movement
SDB	sleep disordered breathing
TD	typically developing
TST	total sleep time
WASO	wake after sleep onset

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* The most important references are denoted by an asterisk.

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<i>Year(s)</i>	<i>Event(s)</i>
1866	JL Down identified DS and its features as a distinct entity ¹⁰
1889	R Caton ⁶⁶ and A Morrison ⁶⁷ described symptoms of patients resembling what we know as “sleep apnea” today; then called “Pickwickians” after a sleepy character in an 1837 Dickens work, referred to by Morrison. One of the characteristics noted of Pickwickians was the presence of overweight.
1924	First EEG, H Berger, published in 1929. ⁶⁸
1935	AL Loomis, EN Harvey and G Hobart showed EEG is vastly different at night. ^{69,70}
1960-1962	First physiological recordings in sleeping Pickwickians (Heidelberg University ⁷¹ and National Institutes of Health in Bethesda ⁷²)
1966	Earliest sleep recordings involving children with DS by Jouvett and Petre-Quaden ⁷³ (in French)
1967	Italian symposia “Bologna group” held first conference to attract sleep researchers—Cornerstone of “Sleep Medicine”. ⁵³
1968	Rechtschaffen & Kales first standardization of criteria used by sleep laboratories to report human sleep scale data, generally used until AASM manual was published ⁷⁴
1969	First sleep recordings of children with DS in the US by Castaldo (Kansas) ²⁸
1970	World’s first sleep disorders clinic opened in US (Stanford) ⁵³
1970s	Basic research in the function of sleep in general. Additional sleep studies of children with DS with primary interest in basic research in sleep staging and characteristics.
1972	Pulse oximetry was developed by Aoyagi and Kishi and was reported in publications in 1975. ⁷⁵
Late 1970s	Airflow, respiratory indicators and peripheral pulse oximetry were added to polysomnography.
1976	First published use of term “Sleep apnea Syndrome” by the “Stanford group” (Guilleminault & Dement) defined based on polysomnographic findings. Half the patients had hypertension, basis of bringing attention later to the cardiovascular disease connection with sleep apnea. ⁷⁶
1980s	Editorials about DS characteristics that predispose children with DS to sleep apnea, example silverman ¹⁷
1987	First PSG study of OSA in DS by Southall ³³
1993	T Young et al. study published in NEJM, brought attention to sleep disordered breathing, and its consequences for the cardiovascular system, in the general population as a public health problem ⁷⁷
2007	The AASM manual for the scoring of sleep and associated events was published

Fig. 1.

Historical timeline of Down syndrome sleep research in the context of general sleep research. AASM: American Academy of Sleep Medicine; DS: Down syndrome; EEG: electroencephalography; NEJM: New England Journal of Medicine; OSA: obstructive sleep apnea; PSG: polysomnography.

Table 1

Studies with polysomnography/polygraphy measuring nocturnal sleep characteristics in children with Down syndrome 1969–2010.

Study Authors Year Location	Participants N Gender Age	Sample selection Inclusion /exclusion	Design (D) Objective (O)	PSG/PG Number (N) Duration (D) Used (U)	Sleep parameters measured/studied Other measures	Findings
Castaldo ²⁸ 1969 US	DS: 10 boys 12– 16 yrs	Institutionalized, normal clinical EEG, not on medications; 2 groups of 5, moderate and severe DD	D: cross-sectional age-matched comparison O: level of DD correlated with REM duration	N: 4 consecutive D: overnight U: nights 2–4	EEG, EOG, EMG D&K criteria, Sleep and REM duration Stanford-Binet IQ	Once in bed no difficulty falling asleep. Lower sleep and REM duration in the severe DD group No statistical significance
Fukuma et al. ²⁹ 1974 Japan	DS: 5 boys, 5 girls 7–17 yrs Endogenous retardation group: 5 boys, 5 girls 7– 17 yrs Normal: 8 boys, 2 girls 8–15 yrs	Both DD groups, institutionalized; Normal group: living at home	D: 3 group cross-sectional comparison O: determine correlation of REM with level of intellectual ability	DS & retardation groups: N: 3 with 7-day intervals U: 2–3 Normal: N: 2 with 7-day interval U: 2	EEG EMG R&K criteria TST, REM, % sleep stage, stage shifts/min, NW/ night, body movements Suzuki-Binet IQ	DS & DD groups mostly in stages 1 and 2; both had longer TST than normal group. DS had higher minutes of time that could not be assessed (indetermined sleep) and greater number of body movements. Lower sleep stage shifts and awakenings in DS. No statistical significance
Petre-Quadens & De Lee ³⁰ 1975 Belgium	DS: 9 neonates, 6 with PSG. Control: 14 normal neonates 11 small-for-date neonates GNS	Unknown criteria, 2 of the infants with DS were cared for by parents	D: longitudinal, started 5HTP between 2 and 6 months, continued administration for 12– 36 months O: effect of 5-HTP on REM sleep and sleep duration	N: 4–19 with unknown intervals D: overnight U: unknown	EEG EOG EMG	Short lasting effect of 5-HTP on increasing REM sleep, muscle tone and improvement of motor behavior in neonates with DS. Abnormal development of sleep spindles likely incompatible with learning. “Probabilistic value” only. No statistical significance
Grubar et al. ³¹ 1986 Italy	DS: 8 boys 8.11 ± 2 yrs)	Institutionalized, DS confirmed by karyotyping, drug-free for at least 2 months, free of medical problems known to affect sleep	D: experimental, pre-post administration of 600 mg BAHs. O: is BAHs associated with increased REM time in DS?	N: 7 consecutive D: overnight U: 2–7 2 & 3 were baseline, 4 & 5 BAHS administration, 6 & 7 no drug	EEG, EOG, EMG Stage % times TST, REM REM latency NW, WASO R&K criteria IQ	7 out of 8 subjects with DS increased their REM time One who did not have an increase had the highest REM at baseline within normal range, indicating a homeostatic limit in REM variation. No side effects were observed.
Gigli et al. ³² 1987 Italy	DS: 5 boys 9.5 ± 2.7 yrs)	Institutionalized, DS confirmed by karyotyping, drug-free for at least 2 months, free of medical problems known to affect sleep	D: experimental Compare baseline, BAHs alone, and BAHS + 6 h intensive didactic program the following morning. O: does BAHs + intensive learning increase REM?	N: 12 nights over a 30-day period D: overnight U: 2–12	EEG, EOG, EMG Stage % times TST, REM REM latency NW, WASO R&K criteria IQ	BAHS alone increased % of REM BAHS + 6 h of intensive learning was associated with reduced TST, increased WASO, increased stage 1 sleep; REM sleep stayed the same improved R. Complete rebound to baseline after cessation of BAHs + intensive learning. No side effects were observed.

Study Authors Year Location	Participants N Gender Age	Sample selection Inclusion /exclusion	Design (D) Objective (O)	PSG/PG Number (N) Duration (D) Used (U)	Sleep parameters measured/studied Other measures	Findings
Southall et al. ³³ 1987 England	DS: 12 1 mo to 6 yrs Controls: 20 age- matched to children with DS GNS	DS: 4 recruited from community for research, 8 recruited after admission to hospital for congenital heart disease and pulmonary hypertension. Controls: random community	D: cross-sectional pilot study comparison at baseline between DS & controls, blinded analysis; pre-post comparison for treatment of OSA; O: prevalence of OSA; effectiveness of treatment for OSA	N: 2 D: overnight (7 ± 2.6 h) U: 2 Setting: DS, 10 in hospital, 2 at home. Control: all at home	SaO ₂ , expired CO ₂ respiratory abdominal movement	50%, of the mostly clinical population with DS (<i>n</i> = 6), had OSA. All OSA cases had abnormal inspiratory resistance and elevated end-tidal CO ₂ ; all but one had hypoxaemia. Treatment with different strategies, depending on patient, ranged from postural changes to adenotonsillectomy. Post treatment there was slight improvement in air flow to complete recovery from UAO, with regression in one patient.
Hamaguchi et al. ³⁴ 1989 Japan	DS: 6 boys, 4 girls 9 mo to 7 yrs Control: 4 boys, 12 girls 5 mo to 8 yrs	DS: unknown if community or institutionalized No congenital heart disease	Cross-sectional comparison of sleep parameter in DS and control O: description of sleep stages and REM in young children with DS	N: 1 D: 326–564 min U: 1	EEG, EOG, EMG, ECG, spiograms % of sleep stages REM REM intervals, NW Body movements Twitch movements R & K criteria “DQ” developmental level (Tsumori-Inage)	2 children had higher REM % and R than controls. 4 children with DS had more body movements than controls. 5 cases showed abnormal patterns of body movements. Fewer twitch movements in children with DS than control. No statistical significance.
Stebbens et al. ³⁵ 1991 England	DS: 20 boys, 12 girls 0–1 yrs and 4–9yrs Control: 15 boys, 11 girls 0–1 yrs and 5–6 yrs	Community, response rate: 94%, all with PSG. One had adenoidectomy, one had UAO as neonate, 12 had congenital heart disease, 12 had other structural defects. Control: random	Case-control comparison of UAO, blinded analysis of sleep measures O: prevalence of UOA by parent and clinical assessment	N: 1, 2 in children under 2 yrs D: 12 h U: 1 & 2	OSA episode = airflow cessation of at least 4 s. Pulse oximetry: SaO ₂ , Chest movements, end- tidal CO ₂ concentration at nostril, clinical assessment. Parent questionnaire: presence of 6 clinical symptoms.	31% of children with DS vs. 4% of control had symptoms of UOA. 41% had increased inspiratory resistance in DS, vs. 3% in control. Increased incidence of stridor in DS. Site of UOA varied. Statistically significant differences between DS and control in episodic oxygen desaturation. Reports on individual cases. 28% of DS cohort eventually had adenotonsillectomy.
Ferri et al. ³⁶ 1998 Italy	DS: 7, gender not specified 8.6–16.5 yrs Control: 6, gender not specified 8– 17.5 yrs	Unknown recruitment. DS: karyotyping, no respiratory illness, no obesity, no abnormal upper airway, no severe macroglossia, no AAI. 2 had heart abnormalities	D: case control comparison of HRV & sleep parameters O: is the heart overburdened by sleep difficulties?	N: 2 nights in lab, but recorded 2nd night only D: overnight U: 1 on 2nd night	Heart rate Sleep structure: stages, stage shifts, WASO, REM latency, NW, TST, SEI, SOL R & K criteria Central and obstructive AHI/hr	Could not stage sleep in all participants, children with DS had reduced HF and increased LF heart rate. Brainstem involvement in central apneas in DS.
Levanon et al. ³⁷ 1999 Israel	DS: 23 1–10 yrs Control: 13 1–10 yrs GNS	DS: referral of family physician or outpatient genetic clinic.	D: cross-sectional comparison O: characteristics of sleep disorders in children with DS.	N: 1 D: overnight, 6–8 h U: 1 Clinic setting	Respiratory disturbance index (RDI) = apnea + hypopnea index; Arousal/awakening index; Leg movements	Time in each stage of sleep not different from that of control. RDI significantly higher in DS. More awakenings and arousals.

Study Authors Year Location	Participants N Gender Age	Sample selection Inclusion/exclusion	Design (D) Objective (O)	PSG/PG Number (N) Duration (D) Used (U)	Sleep parameters measured/studied Other measures	Findings
Dahlqvist et al. ³⁸ 2003 Sweden	DS: 21, 17 with PSG 2–10 yrs Controls: 21 normal siblings GNS	Control: children referred for snoring but were not found to have OSA Community, all families with DS in one city invited. 75% response rate 61% success with PSG. Control: siblings	Associations of respiratory disturbance and arousals, awakenings and movements D: cross-sectional comparison O: prevalence of OSA	N: 1 D: overnight U: 1 Clinic setting	R & K criteria Obstructive apnea episode = airflow cessation of at least 5 s, AHI, total sleep time, snoring, sleep position changes, BMI	24% OSA based on AHI > 1; OSA is not related to DS. Tonsils hypertrophy and higher BMI common in DS are related to OSA. More position changes and snoring in DS. Shorter sleep time in DS.
Dyken et al. ⁴⁰ 2003 US	DS: 9 boys, 10 girls 3–18 yrs	Outpatient population	D: descriptive pilot study O: prevalence of OSA, association with age, obesity	N: 1 D: overnight U: 1 Clinic setting	SaO ₂ , EEG, ECG, EOG, EMG OSA = AHI > 1	79% of clinic population had OSA. No central apneas. There was an association between OSA and obesity, older age, and poor sleep quality.
de Miguel-Diez et al. ³⁹ 2003 Spain	DS: 108 69 boys, 39 girls 1–18 yrs	Patients referred to tertiary care hospital dept of pulmonology	D: cross-sectional descriptive O: prevalence of OSA, association with obesity and age.	N: 1 D: overnight U: 1 Hospital setting	PG OSA = AHI 3 per hour BMI Tonsillar size	54% prevalence of OSA, boys and those 8 yrs old had greater risk. Observed no relation between BMI and OSA.
Mitchell et al. ⁴¹ 2003 US	DS: 23, 11 with PSG 13 boys, 10 girls 1 day–10.2 yrs	All children with DS who were referred to Otolaryngology Dept for UAO	D: retrospective case review O: determine causes of upper airway obstruction in DS	N: 1 D: overnight U: 1 Hospital setting	PSG (no description of sleep parameters or AHI index) Reason for referral, diagnosis, surgical procedures, complications, comorbidities	11 children had OSA, with a majority > 2 yrs. 73% of children with OSA had otitis media. 10 children had laryngomalacia, 1 had inhaled a foreign body, 1 had tracheomalacia. The children without OSA were mostly <2 yrs. Causes and severity of UAO are related to the age of child and comorbidities.
Ng et al. ⁴² 2006 Hong Kong	DS: 15 boys, 7 girls Under 18 yrs Control: 15 boys, 7 girls Under 18 yrs	Community sample, response rate: 6%. Families from DS Association. Control: non-DS, all referred to hospital for snoring Excluded previous adeno-tonsillectomy	D: cross-sectional comparison. Age, gender, weight and height matched controls. O: compare: 1 prevalence of OSA in DS with Non-DS controls who snore, 2 characteristics of OSA vs. No OSA, 3 OSA in DS & Non-DS.	N: 1 D: overnight U: 1 Laboratory setting	S: time asleep, arousal index, AHI, desaturation index, SaO ₂ , during sleep. OSA = AHI > 1.5 Weight for height, asthma, tonsil size & hypertrophy	5% response rate, therefore possibly self-selected for sleep problems. Prevalence of OSA in DS: 59%. Not all children with DS and OSA snore.
Shott et al. ⁴³ 2006 US	DS: 63 56 with PSG Enrolled by age 2 yrs, followed for 5 yrs	Clinic population enrolled following otolaryngological problems	D: 5- year longitudinal prospective cohort	N: 1 or more, not on consecutive nights D: overnight	R & K criteria Sleep duration; percentage of sleep time spent in different stages of sleep;	Parent reports fall short of identifying all children with sleep problems. 54–80% of children had abnormal PSGs.

Study Authors Year Location	Participants N Gender Age	Sample selection Inclusion /exclusion	Design (D) Objective (O)	PSG/PG Number (N) Duration (D) Used (U)	Sleep parameters measured/studied Other measures	Findings
Fitzgerald et al. ⁴⁴ 2007 Australia	DS: 20 boys, 13 girls 0.2–19 yrs	Children with DS who snored and had a PSG, in hospital setting. Exclude previous adenotonsillectomy or CPAP	O: does parental questionnaire predict sleep problems in children? D: retrospective chart review O: association of OSA with snoring. Should those who snore have a PSG routinely?	U: all Clinic setting N: 1 D: overnight U: 1 Hospital setting	number of arousals from sleep Sleep stages R & K criteria. Sleep efficiency, OSA = AHI > 1; Hypopnea = airflow decrease of 20– 50% of baseline amplitude. Significant resp. event if lasted >2 resp. cycles & had 3% fall in SaO ₂ Arousal index	Of the abnormal PSGs only 34% of parents suspected problems. Therefore it is recommended that all children with DS have PSG at age 3–4yrs regardless of history of snoring. 91% were not obese (based on DS growth charts), yet 97% had OSA. Average O ₂ desaturation was 4%, Average AHI index was 12.1. Higher AHI was associated with higher number of arousals. Recommend PSG as a routine for children with DS who snore, regardless of obesity.
Miano et al. ⁴⁵ 2008 Italy	DS: 8 boys, 1 girl 8–20 yrs Control: 14 fragile X 26 normal 30 males 10 females 7–26 yrs	Children attending an educational institute (DS and fragile X). Normal controls from community same region. Excluded obese and OSA	D: cross-sectional comparison. Age & gender matched controls O: manifestation of intellectual disability in relation to sleep architecture	N: 2 D: overnight U: 2nd night Laboratory setting	S: macro- and micro- structures including TIB, TST, sleep efficiency, cyclic alternating pattern (CAP) IQ	Lower sleep efficiency and reduced S2, NREM in DS. Reduction in REM sleep % is associated with intellectual disability.
O'Driscoll et al. ⁴⁶ 2010 Australia	DS: 4 boys, 6 girls Non-DS SDB: 6 boys, 4 girls Normal controls: 2 boys, 8 girls Age: 3–17 yrs	Clinic based recruitment: DS & non-DS referred for SDB; Non-referred normal group	D: cross-sectional comparison of 3 groups O: what is the HR response to arousal in different groups?	N: 1 D: overnight U: 1 Hospital setting	EEG, ECG, EOG, EMG Arousals (ASDA guidelines) Defined mild OSA = 1–5 OAH events per hour; moderate/severe OSA = >5 OAH events per hour	No differences in 3 groups with respect to demographics or BMI. No significant difference between groups in REM, NREM, sleep efficiency, no difference in baseline HR. HR response to arousal in REM and NREM was significantly lower in DS group.
Rosen ⁴⁷ 2010 US	DS: 29 infants under 2 yrs GNS	All infants with DS who were referred to a children's hospital for sleep study 2004–2009	D: retrospective chart review, longitudinal follow-up O: effects of intervention; do infants with DS outgrow OSA spontaneously?	N: 1 or more D: overnight >6 h U: all Hospital setting	EEG, ECG, EMG, EOG, R&K criteria/AASM after 2007 Event defined as chest and abdominal motion with reduction in airflow of 90% of baseline, lasting 2 breath cycles. OSA = AHI > 1	16 of 29 were diagnosed with OSA. One treated with supplemental oxygen at night, 2 adenoidectomy, 4 adenotonsillectomy, 6 CPAP, 3 lost to follow-up. 50% of those treated with CPAP had spontaneous resolution of OSA. Recommend frequent assessment.
Shete et al. ⁴⁸ 2010 US	DS: 7 boys, 4 girls Mean age 8.5 yrs Non-DS: 8 boys, 1 girl Mean age 6.7 yrs	Sleep center patients, selected if had PSG- confirmed OSA defined: AHI > 2, adenotonsillectomy, and follow-up PSG	D: retrospective chart review, pre-post-surgery comparison, comparison with Non-DS O: examine if adenotonsillectomy improves AHI in children with DS	N: 2, pre & post surgery D: overnight U: 2 Hospital setting	EEG, ECG, EOG, EMG, Sleep efficiency AI; R & K criteria. SaO ₂ , oronasal airflow, REM and total AHI	BMI mean: DS 29.8, kg/m ² non- DS 27.6 kg/m ² 60% of DS group had other comorbidities: congenital heart disease, lung disease & immune deficiency. Both DS and non-DS groups had improvements in total and REM

Study Authors Year Location	Participants N Gender Age	Sample selection Inclusion /exclusion	Design (D) Objective (O)	PSG/PG Number (N) Duration (D) Used (U)	Sleep parameters measured/studied Other measures	Findings
Shires et al. ⁴⁹ 2010 US	DS: 52 28 boys, 24 girls 2–18 yrs	One pediatric hospital clinic patients over 10 yrs (1995–2005)	D: retrospective case review O: is higher BMI associated with OSA in children with DS?	N: 1 D: overnight U: 1 Clinic setting	OSA = AHI > 1 RDI 2 resp. events over 2 breath cycles & >3% fall in SaO ₂ . BMI assessed obesity on both DS and standard growth charts	AHI Non-DS group had more improvements, DS group did not improve significantly in lowest SaO ₂ . 63% had OSA. Children with OSA were significantly older and had higher BMI.

5-HTP: 5-hydroxytryptophan; AAI: Atlanto-axial instability; AASM: American Academy of Sleep Medicine; AHI: apnea/hypopnea index; AI: arousal index; ASDA: American Sleep Disorders Association; BAHs: butyramide hydrogen succinate; BMI: body mass index; CPAP: continuous positive airway pressure; D & K: Dement and Kleitman; DQ: developmental quotient; ECG: electrocardiogram; EEG: electroencephalography; EMG: electromyography; GNS: gender not specified; HF: high frequency; HR: heart rate; h: hours; HRV: heart rate variability; IQ: intelligence quotient; LF: low frequency; min: minutes; mo: month; N: number; NREM: non-rapid eye movement; NW: number of awakenings; OSA: obstructive sleep apnea; PSG/PG: polysomnography/polygraphy; R: ratio of oculomotor frequencies; R & K: Rechtschaffen and Kales; RDI: respiratory disturbance index; REM: rapid eye movement; Resp: respiratory; SaO₂ oxygen saturation; Sec: second; SEI: sleep efficiency index; SOL: sleep onset latency; TIB: time in bed; TST: total sleep time; WASO: wake after sleep onset; yrs: years.