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The spectrum of obstructive sleep apnea in infants and children with Down Syndrome

Karen A. Waters[a,b,*], Chenda Castro[a], Jasneek Chawla[c,d]

[a] Department of Sleep Medicine, The Children's Hospital at Westmead, SIDS and Sleep Apnoea Research, Discipline of Child and Adolescent Health, School of Medicine, University of Sydney, Australia
[b] Department of Sleep Medicine, The Children's Hospital at Westmead, Australia
[c] Department of Sleep Medicine, The Children's Hospital at Westmead, Paediatric Respiratory & Sleep Medicine, Queensland Children's Hospital, Brisbane, Australia
[d] Department of Sleep Medicine, The Children's Hospital at Westmead, Faculty of Medicine, Mater Medical Research Institute, The University of Queensland, Australia

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ABSTRACT

Objective: Describe the spectrum of OSA across time in infants and children with Down syndrome.
Methods: Retrospective records review of children who underwent formal polysomnography (PSG) in one of two Australian tertiary sleep centres over selected 3.5-year periods. 152 children were identified, then all sleep study and treatment records were retrieved for the lifetime of the child through 2018.
Results: 3.8 ± 3.2 studies (range 1–17) were retrieved per child and 38.2% had mild disease at worst. Children having only 1 study were more likely to have a normal or mild result than those having ≥2 (chi-square 11.25, *p*-value 0.0008) Studies were more often severe in children age < 2 compared to those ≥2 years, (chi-square 12.87, p = 0.005). After age 2 years, OSA severity increased with age. Amongst 91 (56.4%) children with ≥2 studies, 71 (78.0%) had moderate or severe disease at some time. Studies evaluating the effects of surgery (most often adenotonsillectomy) showed resolution of disease to mild or normal in 53.3%. Where ≥2 studies were evaluated, the last study polarised towards normal or mild disease 40 (44.0%), or treatment titrations 34 (37.4%) with moderate or severe disease in 17 (18.7%).
Conclusions: In a tertiary sleep unit, a full spectrum of sleep disordered breathing in Down syndrome was seen from infancy onwards. Children having only one study were more likely to have normal results. Children with multiple studies reflected disease surveillance, including follow-up after treatment interventions.

1. Introduction

Down Syndrome (DS) is the commonest occurring chromosome abnormality with rates of live birth stable at around 11 per 10,000, including Australia [1,2]. The craniofacial and motor abnormalities in this condition lead to high risk for obstructive sleep apnea (OSA). Prevalence of OSA is higher than in normally developing children where the prevalence estimates are 2–5% with estimates of OSA of around 70%, being severe in almost half, although likely less in population studies [3–6]. In the setting of limited access to sleep studies, it is important that those at higher risk of disease are identified and treated.

It is not clear which subgroups with DS have high risk for OSA, for example particular age groups, or with certain comorbidities. Lin et al.., advocated that all children with DS be screened for OSA as they demonstrate worse gas exchange (higher pCO_2 during sleep and worse McGill oximetry scores) compared to a non-syndromic children [7]. OSA also appears severe in the younger age groups (for e.g. infant < 6months old) [6,8]. A recent study found that the main correlation with age was the timing and type of treatment rather than the occurrence or type of disease [9].

Adenotonsillectomy (AT) remains the most common intervention for OSA, including for children with DS, However, evidence suggests that adenotonsillectomy is often not sufficient to manage their disease, with reports indicating that finding the exact location of ongoing obstruction may require techniques such as sleep endoscopy and MRI [10–13]. Management of ongoing obstruction reported for children with DS, include lingual tonsillectomy and tongue reduction (surgical or coblation), and other therapies including continuous positive pressure ventilation (CPAP/BIPAP), dental appliances, weight loss and nasal steroids [14–16].

This study aimed to delineate the spectrum of OSA in a large cohort of children with DS managed between two Australian tertiary pediatric centres, including evaluation of treatment interventions. We hypothesized that reviewing historical records of children with DS would help

* Corresponding author. Department of Sleep Medicine, The Children's Hospital at Westmead, Locked Bag 4001, Westmead, NSW, 2145, Australia.
E-mail addresses: karen.waters@health.nsw.gov.au, karen.waters@sydney.edu.au (K.A. Waters).

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identify patterns of disease.

2. Methods

This retrospective, descriptive study was undertaken at two tertiary sleep medicine units; the Children's Hospital at Westmead (CHW) and The Queensland Children's Hospital (QCH). The selected 3.5-year period for study for CHW was January 2013 to June 2016, and for QCH from November 2014 to June 2018, inclusive. At each site, the cohort of children was identified through an electronic search of the hospital and departmental records for codes to identify the diagnosis "Down Syndrome" or "Trisomy 21" with a "sleep study" or "PSG" during the relevant period. Polysomnography (PSG) data were collected on all children, from sleep laboratories and medical records. Clinical data including demographics, anthropometric measures, medical history including presence of comorbidities and information regarding treatment recommendations, interventions, and outcomes was obtained from the electronic patient medical record. Once children were identified, all PSG and clinical data for the lifetime of the child, were reviewed through to the end of 2018. The study was approved by the human research ethics boards for each site (LNR/16/SCHN/158 and HREC/16/QRCH/312).

Raw PSG data, held in the archives of each sleep laboratory system, were used wherever possible but for older records study and/or clinic reports were also used, if available. The PSGs were performed in accordance with clinical protocols with sleep state determined by electroencephalography, electrooculography and submental electromyography. Respiratory status was evaluated using pulse oximetry, nasal/oral air flow using nasal pressure, chest and abdominal movements with respiratory inductance plethysmography and carbon dioxide measured using transcutaneous CO_2 ($TcCO_2$). Cardiac rhythm was monitored by electrocardiography. If available, audio and visual recordings were also utilized in the analysis. Studies were analysed using the standards relevant at the time of their acquisition, based on AASM scoring criteria with additional input from the Australasian Sleep Association.

2.1. Statistical analysis

Descriptive statistics were used for patient and clinical characteristics. Categorical variables were described by frequencies and percentages, continuous variables by mean and standard deviation or median and interquartile range. Chi-square tests were used to evaluate differences in group distributions, or t-tests for continuous variables.

3. Results

3.1. Cohort information

Demographics of the children are summarized in Table 1. Full technical reports were available for all PSG studies in the time window for case selection. Characteristics of the individual centres are provided in the online supplement. We reviewed an average of 3.8 ± 3.2 studies (range 1–17) per child and 91 children had ≥2 studies.

Table 1
Patient demographics.

Parameter/outcome	All 152
Gender (%)	Male 89 (58.4) Female 63 (41.6)
Age at 1st PSG (years ± SD)	5.0 ± 4.3 years
Age at last PSG (years ± SD)	8.2 ± 5.1 years
Number of PSG (± SD)	3.3 ± 3.0
Cardiac disease (%)	86 (57.7)
Died (%)	3 (2.0)

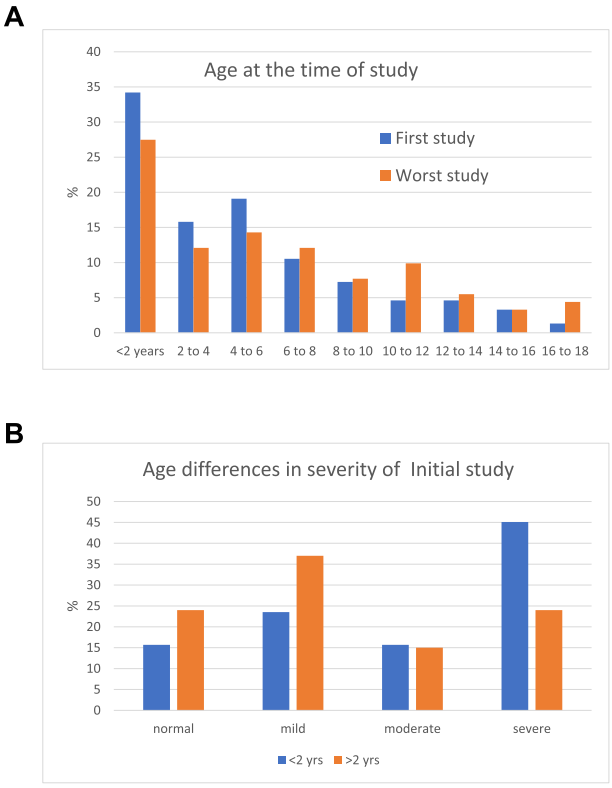

Fig. 1. Patterns according to age. To allow comparison, values in each graph are presented as % of the group in each age category (years).
a. Age distribution of children with Down syndrome, in 2 year intervals, at the time of their initial study (n = 152 cases) or their worst study when ≥2 studies had been undertaken (n = 91). See text for details.
b. Severity of the initial study separated according to age < (n = 52) or > 2 years (n = 100). See text for details.

3.2. First studies

Children's initial PSGs were undertaken at mean age 5.5 ± 4.5 years (range from 1 week–17.8yrs), with a skewed distribution towards infancy (median age 12.5 months, IQR 0–5.7 years), and the number of children having studies decreased with increasing age (p = 0.01). Fig. 1a. For 22 children (14.5%), the initial studies were normal (no OSA), while 52 (34.2%) had mild OSA (OAHI < 5/hr), 30 (19.7%) had moderate OSA (OAHI 5–10/hr) and 48 (31.6%) had severe OSA. Summary data for the initial PSG are provided in Table 2 and Fig. 1a.

At the first PSG, amongst 52 children age ≤2 years, including 21 aged ≤6 months, 4 were obese and 5 had failure to thrive. For the 101 children age ≥2 years, mean BMI z-score was 1.1 ± 1.1 kg/m^2, with 19 children (18.8%) classified as obese (z-score > 2) but only one child (1%) failing to thrive (z-score < −2).

Overall, there was no association between age and the severity of OSA. However, more infants and children age < 2 years had severe disease than those aged ≥2 years (8 normal, 12 mild, 8 moderate and 23 severe compared to 22, 38, 23, and 18, respectively, chi-square 12.87, p = 0.005). Fig. 1b.

Amongst 36 infants ≤12 months of age, there was a diverse pattern of disease and management. At CHW 20 children (28.2%) mean age 5.3 ± 0.4 months, included 13 age ≤ 6 months with 17 (85%) classified as moderate (3) or severe (15) OSA. Six were treated with CPAP, one was treated with oxygen as well as CPAP, and one required Bilevel ventilation for respiratory failure. At QCH 16 children (19.5%) mean age of 6.0 ± 0.3 months included 11 ≤ 6 months with 7 (44%) managed with supplemental oxygen therapy for central disease while 4 (57%) had co-existing moderate-severe OSA.

Table 2
First Study Parameters by centre and by age group. In the Age < 1 and Age < 2 groups. Data for one child at CHW with unrepaired AVSD and baseline saturation values in the 70's were excluded from age-specific groups but included in the full cohort data (CHW and combined).

	Combined (n = 152)	Age < 1 (n = 37)	All age < 2 (n = 52)	Age ≥2 (n = 100)
BMI SDS (age > 2)				1.1 (1.1)
> 2	19 (12.4%)	1 (2.7%)	5 (9.6%)	19 (18.8%)
< -2	1 (0.7%)	4 (10.8%)	4 (7.7%)	1 (1%)
Mod/Severe OSA	68 (44.4%)	25 (68%)	31 (59.6%)	41 (41.0%)
AHI (/hr)	17.9 (26.0)	32.4 (31.9)	26.2 (29.1)	13.9 (23.5)
REM	28.8 (30.0)	45.9 (30.9)	39.3 (31.1)	23.7 (28.3)
OAHI (/hr)	13.1 (22.4)	20.5 (23.3)	16.8 (21.0)	11.3 (23.0)
SaO_2 (%)				
Baseline	95.9 (3.7)	95.5 (5.0)	96.4 (2.5)	95.9 (3.4)
Minimum	81.9 (11.2)	76.6 (11.8)	79.8 (10.2)	83.2 (11.1)
CO_2 (mmHg)				
Baseline	46.7 (4.9)	48.0 (5.9)	47.9 (5.8)	46.1 (4.3)
Retention	72 (47.1%)	21 (56.8%)	39 (61.2%)	44 (44.0%)

3.3. Disease severity across time

For the whole group, 14 children were never diagnosed with OSA. Another 44 children had mild disease at worst, but 44/58 (75.9%) only ever had one study. Amongst 61 children with only one study, 2 had severe disease but died before treatment was instituted or further studies undertaken, and 45 (73.8%) either had no OSA or mild OSA (15 and 30, respectively). Amongst 91 children with ≥2 studies the initial studies showed normal/mild disease in 29 (31.8%) and moderate/severe disease in 62 (68.1%). Over time, 71 of the 91 (78.0%) had moderate or severe disease at some point. Children having only one study were therefore more likely to have a normal or mild result on their initial sleep study than children having two or more studies (chi-square 26.7, *p*-value < 0.0001). Fig. 2a and b.

For the 91 children with ≥2 studies, the worst OSA was seen at mean age 5.9 ± 5.0 yr. The "age of worst disease" was still skewed towards infancy (median 4.9 years, IQR 1.2–9.9 years) and the shift in age from initial studies was borderline for statistical significance (p = 0.055). Fig. 1a. Eight children, initially showing no (1) or mild (7) disease, subsequently developed moderate or severe disease after a delay of 3.3 years, including 4 treated with CPAP. Of 61 children whose OSA was initially moderate or severe, 19 (31.1%) subsequently had normal (2) or mild (17) disease while 35 (57.4%) had ongoing severe disease (6) or ongoing treatment with CPAP (28) or oxygen (1). Fig. 2b. The last studies, in children with multiple studies, were polarised toward normal 40 (44.0%) or treatment 34 (37.4%); 32 CPAP and 2 on oxygen. Chi square compared to the initial study (Chi-square 48.8, p < 0.0001).

3.4. Interventions

Airway surgery was offered in 88 children and undertaken in 84, including adenotonsillectomy (68 or 77.3%), adenoidectomy (11 or 12.5%) tonsillectomy (3 or 3.4%), and tongue reduction (2 or 2.3%) while 4 families (4.6%) declined the surgery. Among children with only one study, 45 had adenotonsillectomy (22 before and 23 after the PSG) and 6 (27.3%) of those who'd had ENT surgery before the PSG had additional surgery after their PSG.

For 37 children, studies were available both before (11.3 ± 14.1 months) and after (11.3 ± 14.7 months) ENT surgery. Table 3. OSA severities prior to surgery included 3 normal, 11 mild, 8 moderate and 15 severe. Post-operative OSA severities were 8 (26.7%) normal, 8 (26.7%) mild, 10 (33.3%) moderate, and 4 (13.3%) severe (chi square 8.7, p = 0.03); 53.3% had either no OSA or mild disease.

Treatments included medications, surgery, CPAP and oxygen. In total, 25 (16.4%) had either no treatment or only medications such as nasal steroids. Another 58 (32.2%) had ENT surgery alone. Most children who had CPAP also had ENT surgery (except infants), and 60 (35.5%) had CPAP recommended at some point, although 7 were awaiting a CPAP trial at the time of analysis. The 53 who had CPAP implemented included 30 (56.6%) considered successful and 9 (17%) partially successful, for a total of 39 (73.6%) with adequate CPAP use. This included 22 (14.5%) who used CPAP temporarily (either pre-

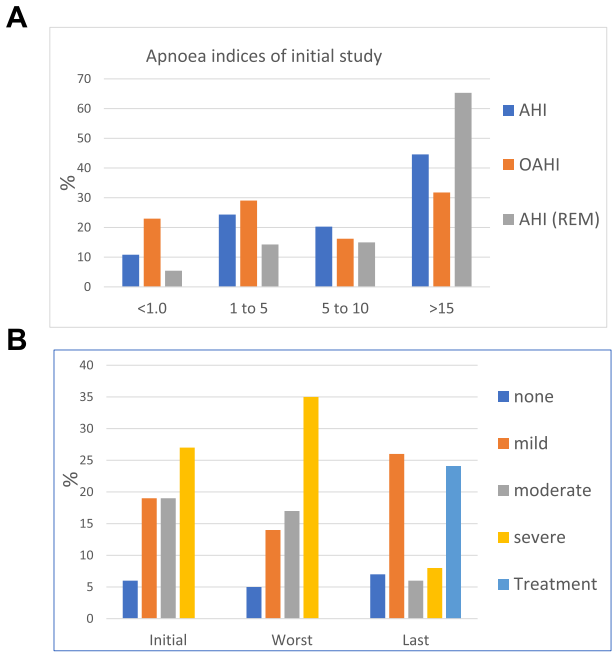

Fig. 2. Proportions (%) with different severities of OSA.
A. Apnoea indices of the initial study for the entire cohort, categories of AHI, OAHI and REM (AHI) values.
B. Changes across time for 84 children who underwent 2 or more sleep studies. Proportions for the diagnostic groups of normal, mild, moderate and severe OSA. Those on treatment at the time of their last study are listed separately. Treatments included nasal mask CPAP and oxygen.

Table 3
Summary of data from 37 children with studies before and after surgery: last study prior to and first study following surgery. Data are presented as mean (Standard deviation) unless otherwise specified.

Parameter	Pre-Surgery	Post-Surgery	p-value
Time from surgery	11.2 (13.8)	11.3 (14.7)	
AHI	16.7 (19.1)	9.2 (8.9)	**< 0.01**
OAHI	12.7 (18.9)	7.1 (8.6)	**0.02**
REM AHI	29.2 (28.1)	20.4 (17.6)	**0.02**
NREM AHI	10.3 (15.6)	5.4 (7.3)	**0.02**
TST	431.5 (98.5)	437.9 (80.9)	**NS**
Efficiency	80.5 (15.0)	85.1 (11.2)	**NS**
% SWS	39.2 (19.8)	39.4 (23.3)	**NS**
% REM	26.8 (10.2)	24.8 (8.9)	**NS**
Arousal index	15.4 (10.9)	10.7 (5.7)	**0.02**
Respiratory Arousal index	6.1 (9.5)	3.4 (3.7)	**0.07**
Baseline SaO_2%	96.2 (4.3)	96.2 (1.6)	**NS**
Minimum SaO_2%	83.2 (10.0)	84.2 (10.8)	**NS**
Desaturation Index	9.4 (6.2)	7.0 (4.6)	**0.06**
Baseline CO_2	47.3 (5.7)	47.0 (4.8)	**NS**
Maximum CO_2	54.2 (9.2)	54.0 (5.7)	**NS**
CO_2 retention in REM (Y:N)	17:20	11:26	**NS**
Severity distribution			
Normal	3	8	Chi-Square 0.08
Mild	11	11	(NS)
Moderate	8	11	
Severe	15	6	

operatively or in infancy) with subsequent resolution of disease, and 32 (21.1%) where it was initiated or continued after surgery. CPAP therapy failed in 11 of the 53 (20.8%) where it was recommended but not established. Additional, sometimes complex, ENT surgeries such as tongue coblation, turbinectomy, and palatoplasty were undertaken in 5 (3.3%) and oxygen therapy was used in 10 (6.6%) including infants and children with pulmonary hypertension. None of the children had tracheostomy.

4. Discussion

This cohort of children with DS, followed from their first diagnostic study, showed a full spectrum of OSA severity; some were never diagnosed with OSA while others had chronic, severe disease. We highlight aspects that are consistent with previous literature, for example OSA occurring in early infancy, and relevant success rates of different therapies, including CPAP and NIV. A high proportion of infants had severe OSA. And, while adenotonsillectomy was often successful in older children, others required ongoing intervention. The profile of this, and other patient populations with DS at tertiary pediatric centres, illustrates a pattern of progress and attendance for these children which we suggest indicates that OSA can be successfully managed in the majority of patients who attend tertiary pediatric services.

This and other studies confirm that, in children with DS, the spectrum of OSA is broad although it is skewed towards severe with 38.6% having moderate or severe disease. In contrast, a multicentre study found only 14% of a population-based group with DS had moderate or severe disease at the age of 3 years [4]. The group presented herein is consistent with other published cohorts of patients referred to specialist centres. Table 4. In summary, amongst 746 children (57% Male), at average age 5.3 years, 23.4% had undergone upper-airway surgery prior to their first study. The first study cleared 29.4% of OSA, so OSA was present in 70.6%. Amongst 627 the breakdown of OSA severity was mild in 35.6%, moderate in 13.4% and severe in 25.2%. The current group confirms that children with only one study are more likely to have a normal result or mild OSA [17]. While we acknowledge that parents' may not perceive the presence or severity of disease [18], it is also possible that those who had normal studies and did not re-present may not have OSA, just as not all children with DS have cardiac disease [19].

Infants < 1year old may have severe disease; Goffinski and colleagues found severe OSA in 71% and our results are similar with OAHI > 10/hr in 26/37 (70.6%) of the same age group [8]. Reported treatments for infants include supraglottoplasty and tracheostomy but these were not used in our group where treatments included only pressure support or oxygen [20]. As Rosen reported, CPAP therapy may be temporary in infants and 6/21 (28.6%) infants we re-studied showed improvement with 47% improved at mean follow-up age 5.1 years (some after adenotonsillectomy), although conversely, 53% had ongoing moderate or severe disease [21].

After initial adenotonsillectomy, OSA was resolved, or mild in 53.3%. Although the overall drop in OAHI for the 37 (12.7–7.1/hr) was modest it is also consistent with other reports [22–25]. Children with DS who undergo adenotonsillectomy may have significant improvement in their OSA although the degree of improvement varies. Recent studies of 20 children each, showed drops of OAHI from pre-to post-operative values of 6.3 to 1.4/hr [9] and 13.75 to 3.5 [24], respectively and 50% of our group had no (23.4%) or mild (26.6%) residual disease [9,24,26,27].

Other surgical options are available if adenotonsillectomy is not curative, and CPAP and NIV were viable therapies in this population [12,28–30]. For those with review, upper-airway surgery and CPAP both resulted significant reduction in the obstructive apnea hypopnea index (OAHI) at follow-up [31]. Reported causes for persistent OSA in DS children include macroglossia (55%), glossoptosis (63%), hypopharyngeal collapse (22%), recurrent enlargement of the adenoid tonsils (63%) and enlarged lingual tonsils (30%) [12]. Children in our group who had persisting disease were most often treated with long term CPAP.

Table 4
Spectrum of OSA in cohorts of children with Down Syndrome.

Author, Year, Country (ref)	Cohort Details (Number, % boys, Mean ± SD age (range), % prior Sx),	Mode (PSG, Plg) % mild, moderate, severe
Miguel-Díez, 2003, Spain[34]	108 (over 2.5 years) 63.9% Male Age 7.9 ± 4.5 (1–18) years 21.3% prior Sx	Plg 35.2% Normal 23.1% mild, 18.6% mod, 23.1% severe
Maris, 2016, Belgium[6]	122 (over 6.25 years) 57.4% Male Age 5.0 (2.8–10.5) years 16.4% prior Sx	PSG 33.6% Normal 19.9% mild, 16.6% mod, 29.9% severe
Hill, 2016, United Kingdom[4]	188 (over 1.5 years) 55% Male Age 3.0 (0.5–5.9) years 16% prior Sx	19 PSG, 169 Plg 27% normal 59% mild, 14% mod-severe
Dudoignon, 2017, France[29]	57 (over 2.5 years) 63.9% Male Age 6.2 ± 5.9 (0.2–24.7) years 32% prior Sx	PSG 19% Normal 24% mild, 18% mod, 39% severe
Nehme, 2018, Canada[1735]	119 (over 10 years) 48% Male Age 6.6 (2 weeks–16.8 years) 27% prior Sx	PSG 44% normal 56% OSA
Waters, 2019, Australia (current)	152 (over 3.5 years) 58.4% Male Age 5.0 ± 4.3 (1 week–18 years) 33.6% prior Sx	PSG 14.5% Normal 34.2% mild, 19.7% mod, 31.6% severe
Total	746 57% Male 5.3 years 23.4% prior Sx	29.4% Normal (of 746) 35.6% Mild } 13.4% Moderate } of 627 25.2% Severe }

|PSG = polysomnography, Plg = polygraphy, prior Sx = prior upper-airway surgery.

We successfully established CPAP therapy in 56.6% where it was attempted and 36 (24%) of the last, repeat studies undertaken were on treatment with oxygen or CPAP. Others report that 30–73% of cases with DS require further treatment for persistent OSA, with recent reports using CPAP, bilevel or oxygen rather than tracheostomy [32,33]. Although it is a selected population, the trend for those with repeated studies was toward improvement. and a high number of children had normal or mild disease on their last study.

The study is limited by its retrospective nature, and represents a selected population attending specialist units where limited access to PSG studies very likely affects the characteristics of the children seen. Not all children were able to be followed or had yet received treatment. Another limitation is our inability to determine whether those who failed to attend subsequent studies were non-compliant rather than improved, although all attempts were made for complete data collection. The possibilities for children who failed to return for additional studies include unrecognised or untreated disease, but they may also be a group showing improvement rather than (even unintentional) neglect.

5. Conclusion

The study provides a snapshot of current patterns for referral, treatment and follow-up in a patient population with DS attending the sleep service at two tertiary pediatric centres in Australia. We confirm

several previous observations regarding the occurrence of OSA and responses to various treatments and conclude DS children are at risk of OSA from infancy onwards. Of those with ongoing monitoring, 78.0% had moderate or severe OSA at some time. A variety of surgical and medical management strategies are available now to treat OSA across the pediatric age spectrum and in this group with DS, we that children with repeated studies showed a trend towards adequate management of their disease.

Declaration of competing interest

There are no conflicts of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijporl.2019.109763.

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