Lower airway pathology in children with Down syndrome

PhD thesis presented on 16/12/2021 at Antwerp University, Antwerp, Belgium.

Mariska De Lausnay [a,b]

Promotors: Kim Van Hoorenbeeck [a,b], Stijn Verhulst [a,b] **Copromotors:** An Boudewyns [c], Marek Wojciechowski [a]

[a] University of Antwerp, Antwerp University Hospital, Department of Pediatrics, Drie Eikenstraat 655, 2650 Edegem, Belgium
[b] University of Antwerp, Laboratory of Experimental Medicine and Pediatrics (LEMP)
[c] University of Antwerp, Antwerp University Hospital, Department of Otorhinolaryngology, Drie Eikenstraat 655, 2650 Edegem, Belgium

mariska.delausnay@gmail.com

Keywords

Down syndrome, airway malacia, respiratory problems

Abstract/introduction

Down syndrome (DS) or trisomy 21 is a prevalent chromosomal disorder that is associated with a broad spectrum of health problems. In children with DS, both upper and lower airway problems are frequently observed and impose a major health burden on both the patients and their families. In this dissertation, we have tried to provide a systematic overview of the different pulmonary and airway problems encountered in this specific patient population, and to explore certain topics in more detail in an attempt to provide a more patient-tailored clinical approach.

PhD summary

First, we made a scoping review of existing literature concerning (lower) airway problems in children with DS. We systematically searched medical databases (MEDLINE and PubMed) to collect relevant papers and were able to include 60 original studies that met our criteria. These were analyzed and summarized by topic. Though a lot of these reviewed papers were retrospective and some of them lacking control groups, they showed consistent conclusions about all of the discussed topics: In DS, airway anomalies (such as laryngo-, or tracheomalacia but also rare combined anomalies) are significantly more prevalent than in controls and often require a specific approach. Furthermore, respiratory tract infections are usually more severe and associated with an increased need for (prolonged) hospitalization. RSV bronchiolitis is a well-studied example of this. A large proportion of DS children suffers from chronic pulmonary aspiration, that is often silent and results in protracted and difficult-to-treat symptoms. Pulmonary hypertension, recurrent wheeze and some other, rare conditions are more commonly encountered in DS. This calls for an increased awareness and multidisciplinary follow-up (1).

Subsequently, we verified the results from previous small-scale studies concerning the higher prevalence of airway anomalies in our DS cohort. We did this in a retrospective manner and added a comparison to a large control group without underlying conditions. We confirmed the presence of one or more airway anomalies in 72% of pediatric DS patients with chronic or recurrent respiratory symptoms undergoing lower airway evaluation (direct laryngoscopy and/or bronchoscopy). This in contrast to the control group, where only 32% had a similar diagnosis. We most frequently encountered airway malacia and found a very high proportion of children with DS diagnosed with multiple airway malformations (about one in four patients) (2).

Since these airway anomalies are associated with a tendency to airway collapse, the question arose whether they have an effect on obstructive sleep disorders in this already predisposed population. It is common knowledge that there is a very high prevalence of obstructive sleep apnea (OSA) in individuals with DS due to the prominent muscle hypotonia, the narrow upper airways and tendency to obesity. However, data on the clinical relevance of lower airway anomalies is scarce. We retrospectively collected data from full overnight polysomnograms (PSG's) from our DS cohort and compared these between the group with lower airway anomalies and the group with a normal evaluation of the lower airways. We found no significant differences in prevalence of OSA, OSA severity or choice of treatment (when comparing a conservative approach, upper airway surgery or CPAP therapy). When looking at follow-up PSG's, there was an overall good response to OSA treatment, again without significant differences between the DS group with and without airway anomalies. We only found a (not statistically significant) tendency to more persistent OSA among those with lower airway anomalies (3).

As we know from our scoping review, children with DS suffer from more (severe) respiratory tract infections, with a higher need for (prolonged) hospitalization. Besides the evident anatomical predisposition, we explored other possible contributing factors. Given that these children receive more antibiotics and spend a lot of time in hospitals and care facilities, we investigated if there are differences in lower airway microbiota. We used the database from the airway endoscopy study and retrospectively added results from bronchoalveolar lavage fluid (BALF) cultures (when available). We compared the detected microorganisms but found no major differences in lower airway microbial composition between the DS group and the control group, besides a significantly higher proportion of DS children with gram negative bacteria such as *Haemophilus influenzae* and *Enterobacterales* (4).

Extensive literature suggests an inherent immunological dysfunction as another possible cause for this increased infectious burden, as well as for the higher prevalence of several autoimmune conditions in DS. Most frequently described in DS are: lower white blood cell count, lower lymphocyte count and several subtypes, abnormal levels of immunoglobulins, and so on. In the search for immunological parameters that are potentially predictive for recurrent infections, we conducted a prospective, cross sectional study. We compared

white blood cell count and differentiation, lymphocyte subgroups and immunoglobulins G, A and M between DS children with and without recurrent respiratory tract infections (RTI's). None of the tested parameters differed significantly between the two groups when accounting for age. We only observed a non-significant trend towards a higher leukocyte and neutrophil count and lower ratio CD4+/CD8+ in the group with recurrent RTI's, but these proved to be poor predictors. Further research (including functional testing) is required, but we suspect that the higher infectious burden in DS children is largely multifactorial in origin.

Another possible contributing factor that should not be underestimated, is chronic pulmonary aspiration (CPA). This remains a challenging diagnosis that is often made indirectly by detection of gastroesophageal reflux and/or by swallowing studies, all with variable sensitivity and specificity. Literature already suggests a high prevalence of dysphagia in children with DS, but the impact on the lungs is yet unclear. We found promising papers concerning biomarkers in respiratory specimens indicating CPA (mostly in experimental settings), and chose to set up a prospective feasibility study determining a number of these biomarkers in BAL samples, namely: lipid laden macrophage index, amylase, pepsin and bile acids. Though some technical issues still need to be addressed, we believe that our suggested future study protocol could benefit not only patients with DS but also with other comorbidities characterized by cognitive or developmental delay in diagnosing CPA.

Based on the findings of this dissertation, we propose the following recommendations (see table 1) which can be helpful in the care of children with DS and chronic / recurrent respiratory problems. Needless to say, these should be tailored to the needs of each individual patient.

As a final **conclusion**, we would like to emphasize that in DS, there is a complex interplay of different organ systems and comorbidities that at times warrant a multidisciplinary approach. So in addition to an experienced general pediatrician who coordinates everyday care for these children, we believe that there should be a close cooperation with a team of pediatric specialists (such as pediatric pulmonologists, cardiologists, ENT specialists, and so on), in order to provide the most optimal care for children with DS.

REFERENCES:

1. Pulmonary complications in children with Down syndrome: A scoping review. De Lausnay M, Ides K, Wojciechowski M, Boudewyns A, Verhulst S. Paediatr Respir Rev. 2021 Dec;40:65-72. doi: 10.1016/j.prrv.2021.04.006.
2. The prevalence of lower airway anomalies in children with Down syndrome compared to controls. De Lausnay M, Verhulst S, Boel L, Wojciechowski M, Boudewyns A, Van Hoorenbeeck K. Pediatric Pulmonology. 2020;1–5. https://doi.org/10.1002/ppul.24741 : sn.
3. Obstructive Sleep Disorders in Down Syndrome's Children with and without Lower Airway Anomalies. De Lausnay M, Verhulst S, Van Hoorenbeeck K, Boudewyns A. Children (Basel). 2021 Aug 12;8(8):693. doi: 10.3390/children8080693. : sn.
4. Lower airway microbiota in children with Down syndrome compared to controls with similar respiratory symptomatology. De Lausnay M, Verhulst S, Boel L, Van Hoorenbeeck K. Transl Pediatr. 2021 Jul;10(7):1818-1824. doi: 10.21037/tp-20-460. : sn.

Table 1. : Recommendations for the care of children with DS and chronic / recurrent respiratory problems

> Refer to / seek advice from a pediatric pulmonologist

> Estimate the need for:

- **Airway evaluation**: keep a low threshold for complete airway endoscopy (especially when the patient presents with stridor or chronic noisy breathing).
- **Polysomnography**: advise a PSG before the recommended age of 4 in case of heavy breathing / snoring, witnessed apneas, excessive daytime sleepiness or behavioral problems. Perform DISE before airway surgery.
- **Evaluation of pulmonary aspiration**: refer the patient to a speech therapist to estimate the risk of dysphagia; keep a low threshold for additional swallow and/or GER studies (even in the absence of indicative symptoms).
- **Immunological screening**, but keep in mind that also asymptomatic children with DS can have e.g. leuko- and/or lymphopenia.
- **Screening for pulmonary hypertension** in consultation with a pediatric cardiologist since no formal guidelines exist; a cautious proposal would be to perform an annual cardiac ultrasound until school age and further every 5 years (also in the absence of cardiopathie congénitale).

> Check the vaccination status; advise influenza vaccine annually and 23-valent pneumococcal vaccine for patients >2y with chronic cardiac or pulmonary disease

> In case of need for anesthesia, keep in mind the risk of difficult intubation due to tracheal narrowing and/or the possible presence of airway anomalies