

Respiratory Infection in Children with Down Syndrome

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Published Date: April 11, 2017

ABSTRACT

Down Syndrome (DS) is the most common genetic disease and presents with cognitive impairment, cardiac and gastrointestinal abnormalities, in addition to other miscellaneous clinical conditions. Children with DS have an increased risk of infections, especially respiratory tract infections, which can be of diverse pathogenic origin (e.g. viral, bacterial, fungal or a combination of these). This increased susceptibility to infections has been linked to abnormal parameters of the immune system. DS is the most common recognizable genetic syndrome associated with immune defects. The abnormalities of the immune system associated with DS include; mild to moderate T and B cell lymphopenia, marked decrease of naive lymphocytes, impaired mitogen-induced T cell proliferation, reduced specific antibody responses to immunizations, and defects of neutrophil chemotaxis. Infections in DS are characterized by increased severity and prolonged course of disease, and a slower resolution of illness as compared to other children. This chapter will address the infectious diseases in Down syndrome children and immunological and non-immunological factors involved in the pathogenesis of these diseases.

Keyword: Down syndrome; Infections; Immunodeficiency; Respiratory tract infections.

INTRODUCTION

In 1886, Down described clinical characteristics of the syndrome that now bears his name. In 1959, Lejeune and Jacobes et al independently determined that trisomy 21 is the cause. Down syndrome (**DS**) is by far the most common and best known chromosomal disorder in humans and the most common cause of intellectual disability [1]. The Down syndrome patient has clear anatomic differences in the head and neck region when compared with the general population. These anomalies included a flat occiput, oblique palpebral fissures, epicanthal fold. Speckled irides, a protruding tongue, prominent malformed ear, and a flat nasal bridge [2].

Hearing impairment and ontological problems including otitis media are still found in 38-90 % of children with DS compared to 2.5% of normal children. In DS, there is a clear increased incidence of congenital temporal bone anomalies, external auditory canal stenosis, mid-facial hypoplasia, poorly functioning Eustachian tube, comparatively small postnasal space, poor muscle tone transmission rate that are accelerated at the brainstem or delayed at the cortex and weak immunity [3].

Down syndrome is the most common chromosomal abnormality among live-born infants. The incidence is estimated to be one in 600 to one in 900 in the United States. DS is also the most frequent genetic cause of mental retardation and is associated with a high incidence of congenital cardiac and gastrointestinal tract anomalies [4]. Down syndrome is the most common whole chromosomal aberration managed in otherwise healthy neonates. It has been extensively documented that DS children have an increased incidence of respiratory tract infections compared with non-DS children, in addition to a myriad of their other health complications [5,6]. Respiratory tract infections, particularly otitis media, have been identified as one of the most significant health problems in DS children of school age by their parents, with a higher frequency than in the general population. This increased susceptibility to infections have been linked to abnormal parameters of the immune system for more than 30 years, and DS is the most common recognizable genetic syndrome associated with immune defects. Moreover, various medical and anatomical co-morbidities commonly associated with DS increase the susceptibility to infections and might also affect the immune responses [7-9].

Multiple hypotheses were postulated to describe why DS patients are more susceptible to respiratory infections, including anatomical abnormalities, gastro esophageal reflux, and neurological and immunological etiologies. Hypotonia may contribute to the neurological pathogenesis, whereas macroglossia, tracheomalacia, and gastroesophageal reflux, leading to aspiration, may all contribute to the anatomical causes of increased respiratory tract infections. There have been many studies describing the immunological changes in DS patients compared with non-DS patients [10,11].

RESPIRATORY TRACT INFECTIONS

Down syndrome children are known to suffer from more frequent infections than normal children, and most studies agree that the most common cause for acute hospital admission in DS children is lower respiratory tract pathology, including pneumonia, bronchiolitis, and croup. Selikowicz [12] has used a parent questionnaire and reported that the prevalence of significant lower respiratory illnesses among DS children was 8%. Hilton and his colleagues [13] have comprehensively reviewed 232 hospital admissions among DS children over a 6.5 year period and found that lower respiratory tract pathology was the most common cause for acute hospital admission.

A higher incidence of acute lung injury secondary to pneumonia was found among DS children when compared to normal control children. A subsequent study examined 24 consecutive children with DS and 317 children without DS who were admitted to the pediatric intensive care unit (ICU) for mechanical ventilation [14]. In that study, 58% of DS children and 13% of non-DS children met criteria for acute lung injury. Similarly, 46% of DS children and 7% of non-DS children were diagnosed with acute respiratory distress syndrome (ARDS). None of the DS children in this cohort with acute lung injury died, whereas others have reported a mortality rate of about 5% of non-DS children with ARDS. These data suggest that children with DS have an increased risk of progressing towards ARDS, although with low mortality, and support the hypothesis of abnormal regulatory mechanisms of inflammation, such as an imbalance of anti-oxidants and oxidative stress [15], which might lead to apoptosis in lung tissue.

A review of a large cohort of DS children in Sweden and Denmark [16] revealed a 12-times increased risk for mortality due to infections, especially septicemia. This excess of mortality was consistent with data from a recent study in which DS children showed a 30% higher risk of fatality secondary to sepsis when compared to other children hospitalized for sepsis [17], after controlling for confounding factors including pathogens and co-morbid conditions.

The above mentioned studies highlight the increased frequency and severity of respiratory tract infections in DS children. These are predominantly ear infections; however, pneumonias occur frequently in children younger than 5 years of age and are likely to require hospitalization. Lung disease might be of more prolonged duration and might progress to ARDS. In addition to respiratory tract infections, periodontal disease is another condition of infectious aetiology that occurs frequently between 58% and 96% of individuals with DS [18]. Due to the complexity of the pathophysiology of gingivitis, the contributions of potential determinant factors such as abnormal immunity and poor oral hygiene have not yet been defined clearly.

The most common bacteria known to cause acute otitis media and pneumonia in children are the *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. There are also few studies on the pathogens causing recurrent respiratory infections or otitis media in DS children,

with isolated case reports that describe uncommon aetiologies (i.e. *Bordetellabronchiseptica*), which probably do not represent the large majority of infections among DS children. Of more relevance, changes in the frequency and microbiology of infections after the introduction of the recommended anti-pneumococcal immunization in 1999 have not been studied in this patient population [19,20].

Respiratory syncytial virus (**RSV**) is a common virus that everybody encounters, which can cause severe infection in high-risk infants. RSV is known to be the most important and severe cause of lower respiratory tract infections in all children, and certain groups (e.g. preterm infants) are identified early in infancy to have a high risk of RSV infection and receive immunological prophylaxis against this disease. Of note, a subsequent study [21] showed that hospitalization for RSV-induced lower respiratory tract infection in children with DS did not increase significantly the risk for recurrent wheezing or long-term airway morbidity. This study reported that the incidence of recurrent wheeze was higher among DS children at about 30%, regardless of whether or not they had a history of RSV-induced lower respiratory tract illness. Megged and Schlesinger [22] pointed out that DS infants with RSV are older and require longer hospitalization than non-DS infants, possibly reflecting the association with cardiac disease. More recently, a study of health services utilization by a cohort of DS subjects in Western Australia compared surveys conducted in 1997 and 2004. The study noted a reduction of the incidence of overall infections, but mainly upper respiratory infections. Further analysis of association with other clinical findings showed that the decrease of ear infections was seen only in DS patients without heart disease. Pneumonias, tonsillitis and bronchitis were observed to have a decreasing trend in both groups with and without heart disease, suggesting that cardiac function was not a determinant of the risk of infections [22].

RSV bronchiolitis is a major health issue in DS children, as it accounts for 17.6% [22] of all DS admissions to hospital compared with 7%-9% [23] overall. The incidence of hospitalization for RSV infection in children with DS in large cohorts is 9.9%-17.6%, which is higher than the hospitalization rate (1%) in the normal population [22,23]. RSV cannot be cured and can only be prevented. RSV management includes education of parents on how to prevent infection, the implementation of good hand hygiene, and/or the monthly administration of palivizumab (a monoclonal antibody against the RSV-F protein) during the RSV season. This humanized monoclonal antibody neutralizes the virus as it binds to the antigenic site of the F-fusion protein of RSV. The fusion protein neutralized both RSV serotypes A and B. Palivizumab has become the mainstay for infants with other risk factors for severe RSV bronchiolitis, such as congenital heart disease, chronic lung disease, and prematurity. In those infants, palivizumab has proven to reduce hospitalization rates by 39%-78% [24]. Moreover, it has recently been shown that palivizumab treatment reduces the wheezing days in otherwise healthy-late preterm infants [25,26].

The increased risk of infections in DS children has been attributed to immunological defects and to the airway and other associated abnormalities. Defects in immunological parameters in DS have been described and postulated as explanations for the increased severity of infections seen in DS children [8,9]. Reduced ranges of the different lymphocyte subsets were found to be of most significance in childhood, with subsequent improvement over age. T and B cell subsets are decreased below the 10th percentile of normal in almost 90% of DS children, and below the 5th percentile of normal in 60% of them. The normal early T cell expansion in infancy was not observed. Their thymus size was reported to be smaller than non-DS children, with decreased T cell percentages bearing the T cell receptor **(TCR)**- $\alpha\beta$ and relatively reduced naive T cell percentages [27-29], resulting in mild to moderate lymphopenia. Kuester et al. [30] have reported that lymphocyte subsets of 95 DS children visiting their centre for follow-up of their thyroid function and 77% of patients had frequent respiratory infections. In this cohort, 57 (60%) of the children were aged 5-16 years, and only three children were above 16 years of age. The number and percentage of naive T cells were decreased approximately by half across the age-ranges compared to non-DS children, although they did not reach severe immunodeficiency levels. For example, the median naive CD4 T cells in 5-10-year-old children was 280 cells/ μ l (44% of CD4 T cells) for DS and 730 cells/ μ l (72% of CD4 T cells) for age-matched controls. There was no association of low T cell counts and the presence of recurrent infections. Memory T cell percentage and count were not significantly different from normal controls, an argument that the study authors used to postulate the presence of an intrinsic immune defect that renders those cells impaired to control infections. In the same DS cohort, the investigators compared several maturation stages of peripheral blood B cells with those of normal children and found decreased numbers of all B cell stages, particularly naive B cells [31].

Innate immune defects have also been also studied in DS individuals in the late 1970s and differences in neutrophil chemotaxis have been reported in several studies [32-34], and they did find significant reduction in chemotaxis activity in DS children. Other neutrophil functions such as phagocytosis and oxidative burst responses were not consistently reported to be affected in these studies [35,36]. Studies of the integrin β -2 (CD18) in DS blood cells were conducted when the gene encoding this protein was located to chromosome 21. The initial studies of CD18 expression in DS individuals using lymphoblastoid cells reported increased cell surface expression and cell aggregation [37,38]. Other studies [39,40], however, reported that the increased expression does not occur in non-transformed cells.

Studies using only CD56 as a surface marker for natural killer (NK) cells suggested that these cells were increased in peripheral blood of DS children [41]. The absolute numbers of NK cells has been demonstrated in some studies [42] to be low in DS children, and this discrepancy was attributed to the difference of surface markers used. Also, the observed disturbances in the secretion of cytokines interleukin **(IL)**-2, IL-7 and IL-10, and deficiency of mannan-binding proteins have been suggested to contribute to the increased susceptibility to infections [43,44].

Anatomical abnormalities of the airways associated with DS may be an important factor predisposing to increased risk of infections, particularly respiratory tract infections. These abnormalities may impair clearance of secretions and facilitate infections. Airway anomalies have been reported among 75% of DS children and 35% of non-DS children with recurrent respiratory symptoms who underwent fiberoptic bronchoscopy [45]. Laryngomalacia was the most common airway abnormality, with 50% incidence in the DS group compared to 19% in the non-DS group. Tracheomalacia and tracheal bronchus, and pulmonary hypoplasia have also been reported in DS children [46,47].

The incidence of airway obstruction and obstructive sleep apnoea is found to range from 63% to almost 80% in DS children [48]. Predisposing factors that lead to obstructive sleep apnoea in DS include the characteristic mid-face hypoplasia, tongue enlargement and mandibular hypoplasia. This small upper airway, combined with relatively large tonsils and adenoids, contributes to airway obstruction and increases susceptibility to infections. Upper airway obstruction due to adenoids and tonsillar hypertrophy was reported in 30 (6%) of 518 DS children seen consecutively [49]. Those with severe obstructive symptoms, e.g. snoring, were found to be more likely to have tracheobronchomalacia, laryngomalacia, macroglossia and congenital tracheal stenosis. Five patients required tracheostomy because of persistent obstruction.

One of the most important predisposing factors to respiratory tract infections in DS children is the gastro-oesophageal reflux. Gastro-oesophageal reflux may result in aspiration of gastric contents into airway causing lung inflammation or a reflex mechanism of the lower oesophagus triggering bronchospasm [50]. Several studies have documented that the recurrent aspiration of thin fluids is well known to be associated with increased incidence of lower respiratory tract infections [51,52]. The hypotonia associated with DS includes poor pharyngeal muscle tone that increases the risk for aspiration [53]. Subclinical aspiration may account for up to 42% of cases of chronic respiratory complaints in DS children compared to only 12% in non-DS children, [54,55]. Zarata et al. [56] has reported that esophageal motor disorders, particularly achalasia, are frequent in individuals with Down's syndrome. Awareness of esophageal dysmotility in this population is important, and DS children would benefit from evaluation of swallowing function [56,57].

External ear canal stenosis is found to be present in up to 40-50% of DS newborns [58]. The Eustachian tube may also be of small width, contributing to the collection of middle ear fluid and chronic otitis media [59]. Recurrent acute otitis media is a particularly frequent problem, affecting one half to two thirds of DS children, leading to conductive hearing loss in as many as three quarters of these children. Otitis media with effusion is the most common cause of hearing loss and the delayed development of language reported in DS children [60]. In Glasgow, the prevalence of otitis media in DS was 39% at one year of age, falling to 68% by age of 5 years [61]. Children with Down syndrome who are found to have a hearing loss due to otitis media should be

identified early and be provided with a means to either restore their hearing or to be fitted with hearing aids

In summary, children with DS are at high risk of respiratory tract infections partly due to the associated adaptive and innate immune defects and partly to airway and other associated abnormalities. Investigations of DS children with history of increased frequency of infections for immunological and non-immunological factors that increase the risk of infection are recommended. Also, Identification of factors responsible for these recurrent infections could facilitate further improvement in survival and decreasing mortality of children with Down's syndrome.

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