Host immune response in children with Down syndrome related to respiratory tract infection

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Chapter 7

General discussion

Case report

Nicholas, an 18-month-old infant with Down syndrome, was referred by his family physician to a paediatrician because of recurrent lower respiratory tract infections. He has received all the regular vaccinations for his age. His growth chart is +0.5 SD for his age (growth chart for children with Down syndrome). A cardiac ultrasound performed at birth was unremarkable. On physical examination, we observe a child with mild rhinitis. It is difficult to examine his eardrums due to his small external auditory canals. Auscultation of the lungs reveals a slight wheezing. He has some tachypnoea, no dyspnoea. No cardiac murmur is heard. The examination of the abdomen is normal. On neurological examination, he shows truncal hypotonia. He can't sit yet without support. The paediatrician decides to perform blood tests: blood leukocyte count and differentiation, B and T cell counts and antibody levels (IgA, IgM, IgG and IgG subclasses). This reveals leukopenia with lymphopenia, low T and B cell counts and low levels of IgG2 and IgG4. A chest X-ray reveals an infiltrate in the right upper pulmonary lobe, as has been seen in a previous X-ray. The paediatrician prescribed amoxicillin-clavulanic acid for one week, followed up by cotrimoxazol to prevent further upper airway infections. The patient was then referred to a paediatric pulmonologist, who decided to perform a laryngotracheobronchoscopy in order to exclude anatomical abnormalities of the respiratory tract. During bronchoscopy, a tracheal bronchus was found, a congenital abnormality in which the right upper lobe of the lung has its origin in the trachea rather than distal to the carina; this condition may be associated with right main bronchus stenosis and may cause recurrent right-sided pneumonia. Nicholas recovered well, and is now a thriving 3-year-old without any antibiotic prophylaxis.

Children with Down syndrome have an increased risk of developing respiratory tract infections, as compared to other children.[1] Several factors contribute to this enhanced vulnerability, as shown in Figure 7.1. The left side of this figure, which is a graphical abstract, presents the pathophysiological mechanisms of respiratory tract infections in Down syndrome. Three main causes are identified: anatomical defects, neurological impairment and immunological defects. The right side of the figure shows the factors responsible for the quality of medical care: multidisciplinary care in specialist medical facilities, transmural care, patient organizations, infection prevention, early diagnostics and clinical research. The section below will discuss pathophysiology and is followed by a section dealing with the quality of medical care.

Pathophysiology

Children with Down syndrome have anatomical alterations of the upper and lower respiratory tract, which may contribute to an increased risk of respiratory tract infections. These are: a) mid-face hypoplasia; b) external ear canal stenosis; c) a comparatively smaller trachea and; d) laryngomalacia and tracheobronchomalacia and e) abnormally shaped alveoli in the lungs.

Mid-face hypoplasia alters the nasopharynx area, where the Eustachian tube opening is located. This, together with dysfunction of the tensor veli palatine muscle (due to hypotonia) causes distortion of the air pressure equilibrium within the middle ear, resulting in fluid accumulation in the middle ear and chronic otitis. External ear canal stenosis causes cerumen impaction in some 50% of newborns with Down syndrome and makes it difficult to diagnose otitis. In light of that, it is possible that the presence of otitis media is underestimated in Down syndrome, and consequently, that it is under treated.[2] Another anatomical alteration is the smaller trachea that children with Down syndrome have as compared to other children. In Down syndrome, one of the congenital abnormalities of the trachea is a tracheal bronchus (a condition where the right upper lobe of the lung has its origin in the trachea rather than distal to the carina. This condition could be associated with right main bronchus stenosis, which, in turn, may cause recurrent respiratory tract infections).[3] Laryngomalacia and tracheobronchomalacia are additional anatomical factors that contribute to respiratory tract infections. Finally, children with Down syndrome are prone to have abnormally shaped alveoli in their lungs, as well as a smaller number of them. These findings may be related to respiratory morbidity in Down syndrome.[4]

Aside from anatomical abnormalities, the neurological deficits in Down syndrome described in Chapter 2 of this thesis play an important role: these children present with general hypotonia. Consequently, they have a diminished capacity to cough effectively, which then results in sub-optimal clearance of sputum and microbes from the respiratory tract when respiratory tract infections develop. Hypotonic children are also prone to silent (micro) aspirations of fluids, food and saliva, due to swallowing dysfunctions. This factor also lends itself to the development of respiratory tract infections (mainly with anaerobic bacteria, that are present in the oral cavity).[1,5]

Alterations in innate immunity are a third category of factors that make children with Down syndrome more vulnerable to respiratory tract infections. Clinicians are well aware of the impact that a lower respiratory tract infection can have in these children. Their clinical condition can quickly deteriorate, requiring transfer to an intensive care unit for artificial ventilation. To counter this problem, we set up a collaborative study with Professor Tom van der Poll's lab in the Center for Experimental and Molecular Medicine at the Academic Medical Center. We performed in vitro studies with pathogens that can cause a severe pneumonia, based on the hypothesis that this could give us insight into the pathophysiological mechanisms of the immune response in children with Down syndrome. To this end, we chose the following pathogens: influenza A virus, pneumococci, and lipopolysaccharide (an important component of a Gram-negative bacterium). This selection enabled us to compare the effect of a Gram-positive bacterium, a Gram-negative bacterium and a virus on the immune system of children with Down syndrome. Naturally, we realize that ideally, these studies should have been performed using broncho-alveolar lavage fluid from these children. However, this was not possible due to the low total number of children with Down syndrome on artificial ventilation. Moreover, since this is quite an invasive procedure, it would have been difficult to obtain ethical permission for the study. As noted in Chapter 3 of this thesis, we found that children with Down syndrome in vitro show a different cytokine response after stimulation with heat-killed pneumococcus, indicating that they have an abnormal innate immune response. This is mainly due to high levels of IL-10 which can compromise the immune response and thus lead to more severe pneumococcal pneumonia.[6] Chapter 4 describes how children with Down syndrome have an increased pro-inflammatory response to live influenza A virus after in vitro stimulation. This causes more severe local inflammation and may lead to more damage of the respiratory epithelium.[7] In clinical facilities during the 2009 H1N1 pandemic in Mexico, Down syndrome patients did, in fact, prove to be at high risk for adverse outcomes, such as hospitalization, endotracheal intubation and death.[8]

Children with Down syndrome, including those without a congenital heart defect, have an enhanced risk of developing a severe Respiratory Syncytial Virus infection.[9] This may be due in part to an abnormal innate immune response, in which the influx of granulocytes plays an important role.[10] Chemotactic migration of polymorphonuclear leukocytes is reduced in Down syndrome.[1,11]

A fourth category of vulnerability factors for respiratory tract infections is related to the abnormal adaptive immunity of children with Down syndrome. Chapter 5 reports on the higher frequency with which children with Down syndrome have respiratory tract infections, as well as their lower levels of: IgG2; total lymphocytes; B and T lymphocytes and iNKT cells and regulatory T cells, (probably due to diminished production and proliferation in the thymus).[12]

Children with Down syndrome commonly have high levels of IgG and IgA, with high levels of IgG1 and IgG3 and low levels of IgG2 and IgG4.[13-15] These altered IgG levels are most likely due to dysregulation in class-switching and somatic hyper mutation of B lymphocytes in the germinal centres rather than impaired B lymphocyte production in the bone marrow.[16,17]

In patients with Down syndrome, an increased Th1/Th2 ratio has been reported. Th1 are Helper T lymphocyte type 1 cells that stimulate IgG1 and IgG3 production. Th2 are Helper T lymphocyte type 2 cells that stimulate IgG2 and IgG4 production. This may explain why IgG1 and IgG3 production is higher, whereas IgG2 and IgG4 production is lower in Down syndrome.[18]

The combination of deficient T cell counts and function, B lymphocytopenia and a lower number of switched memory B cells specific for vaccine antigens may cause an inadequate vaccination response in Down syndrome: children with Down syndrome produce diminished antibody levels after vaccinations against tetanus toxoid, *N. meningitides* type C and H1N1 (influenza A virus), but not against pneumococcal polysaccharide.[16,19-22]

Quality of medical care

The long history of medical care for children with Down syndrome has not only increased knowledge of different aspects of their medical care, but has also led to recognition of their need to visit multiple doctors. Over the past decades, as advancements have increased in medical care, (e.g. the early treatment of congenital heart defects), the average life expectancy of children with Down syndrome has risen dramatically. Parents, in combination with

patient organizations for Down syndrome, are calling for more integrated medical care. In the Netherlands, guidelines for this type of medical care have been adapted accordingly.[23,24] This has been done in conformity with international guidelines on coordinated care for these children.[25-27] The Down Expertise Center at the outpatient paediatric clinic of the VU Medical Center consists of a multidisciplinary team of specialists (paediatrician, physiotherapist, paediatric cardiologist, otorhinolaryngologist, paediatric infectologist, ophthalmologist and pulmonologist), who are available to evaluate children with Down syndrome. Other specialists, including a paediatric urologist, a paediatric surgeon and a paediatric orthopaedic surgeon are available for consultation, if necessary.

In 2015, Professor Esther de Vries, a paediatric infectologist/immunologist, introduced a concept of integrated care for children with Down syndrome, comprised of a transparent organization model for transmural care. At present, efforts are underway to inform caregivers of children with Down syndrome about this innovative approach to medical care. The complete chain of care has been addressed to optimize the medical treatment these children receive. The goal is to improve coordination between primary care physicians, hospital-based physicians, paramedical professionals, the patients and their families.[25,28]

In addition, *Stichting Down Syndroom*, a Dutch non-profit patient organization plays an important role in providing information to the public, as well as to parents and caretakers of children with Down syndrome. Established 25 years ago by the parents of a child with Down syndrome, this organization boasts an extensive network of parents and caretakers of children with Down syndrome throughout the Netherlands. The organization believes strongly in coordinated care. They organize symposia, in addition to developing and supporting research. They also edit a journal "Down + Up" with information about Down syndrome.

Children with Down syndrome who suffer recurrent respiratory tract infections, have anatomical abnormalities of the respiratory tract, and have difficulty evacuating sputum or have immunological defects, sometimes receive trimethoprim/sulfamethoxazole prophylaxis, especially during the winter months. Although some research has concluded that trimethoprim/sulfamethoxazole prophylaxis diminishes the frequency of RTIs in children,[29,30] no studies have been conducted as yet to demonstrate the possible effect of these indications in children with Down syndrome. However, our clinical experience indicates that this antibiotic prophylaxis has a positive effect on the incidence of respiratory tract infections in these vulnerable children. For this reason, we also recommend it for some children with Down syndrome. Future research is needed to determine whether the use

of antibiotic prophylaxis in Down syndrome diminishes the frequency of upper and lower respiratory tract infections.

As described earlier in this chapter of this thesis on the immunological aspects of respiratory tract infections in children with Down syndrome, the impaired response these children have to vaccinations will not protect them adequately against respiratory pathogens. The Netherlands has a highly effective vaccination programme that offers all children free inoculations. Moreover, the Dutch Health Service (Gezondheidsraad) plays a very active role in recommending which new vaccines and vaccination schedules should be implemented in the nationwide vaccination programme. The Health Service's role offers an opportunity to introduce a tailor-made vaccination schedule for children with Down syndrome, which could consist of booster vaccines or other adjustments to the current vaccination schedule. Passive immunization against RSV in young children with Down syndrome, even those without a cardiac history, should be considered, as Down syndrome is an independent risk factor for developing severe RSV bronchiolitis.[9] Additionally, an influenza A vaccination is recommended annually for children with Down syndrome, and may even need to be administered more than once a year, as these children's antibody response might be insufficient.[21]

It is important to perform more clinical studies in this area.

Early diagnostics are important. As was the case with Nicholas (the patient with Down syndrome discussed earlier who suffered from recurrent respiratory tract infections), immunological work-up, X-rays and bronchoscopy should be considered in an early stage of the disease. Nicholas may show immunological impairment in his innate and adaptive immune response that is typical of children with Down syndrome, and that will increase his risk of developing respiratory tract infections. For the immunological work-up, we would recommend the guidelines of the ESID, European Society for Immunodeficiencies.[31] Furthermore, it is important to perform radiological studies (mainly chest X-rays, and less frequently CAT scans) and compare these with former studies, if available. Recurrent lower respiratory tract infections in the same pulmonary lobe may indicate abnormal anatomy of the respiratory tract. Consultation with the otorrhinolaryngologist and the paediatric pulmonologist is recommended: the trachea of children with Down syndrome is smaller than those of other children. In Down syndrome, one congenital abnormality of the trachea is a tracheal bronchus (a condition where the right upper lobe of the lung has its origin in the trachea rather than distal to the carina). This condition may cause recurrent RTIs of the right upper lobe of the lung. Laryngomalacia and tracheobronchomalacia are additional

anatomical factors that contribute to RTIs.[4] A laryngotracheobronchoscopy should be considered to exclude these anomalies. Consultation with a paediatric physiotherapist is also recommended, as can be seen in the example from our case study. Nicholas is hypotonic, a neurological deficit associated with Down syndrome that plays an additional role in the development of respiratory tract infections. Since this condition diminishes the patient's capacity to cough effectively, it also hinders the expulsion of sputum and microbes from the respiratory tract in the presence of developing respiratory tract infections. In light of that, it is important for a paediatric physiotherapist to evaluate the patient's motor development level and advise the parents on how to stimulate their child's motor skills.

Clinical research is also needed. We would recommend that future studies be conducted as multi-centre studies. This will be possible in the near future now that the DOC (Downteam Onderzoeks Consortium), a national organization in the Netherlands, has been founded and has established collaboration between Down syndrome patients, their parents, healthcare professionals and researchers. Working together, these parties define care guidelines for Down syndrome patients and promote research projects. The DOC's focal project is an online database, Digidown, which compiles data about medical problems, treatment and results. Furthermore, the Trisomy Research Society provides an excellent opportunity for researchers to meet each other and conduct research on Down syndrome through international collaboration.

It is very important to generate financial funding to support research development. Fortunately, a number of European funds are currently available for this purpose, such as the Horizon grants and subsidies.

Future studies are needed to determine whether use of antibiotic prophylaxis in Down syndrome will diminish the frequency of upper and lower tract RTIs. For example, it would be interesting for a paediatrician and an otorhinolaryngologist to follow a cohort of young children with Down syndrome (0–4 years old), checking their history of otitis systematically every 3 months, evaluating their immune status, performing otoscopy and audiologic tests and evaluating the need for adenotomy and ventilation tubes and/or antibiotic prophylaxis. This is important in order to gain a broader picture of the problem of otitis in children with Down syndrome. It will also help to evaluate whether surgical intervention and/or antibiotic prophylaxis will contribute to better physical health and quality of life for children with Down syndrome, as achieving that is important to optimizing their general and speech development during this very crucial stage of their lives.

Main conclusions

1. Children with Down syndrome suffer more frequently and more severely from respiratory tract infections than do other children.

2. These respiratory tract infections are mainly of viral origin. The most commonly described is RSV bronchiolitis in young children with Down syndrome. However, patients with Down syndrome also contend with influenza A virus infections.

3. Several therapeutic strategies are possible to prevent these respiratory tract infections:
   - Trimethoprim/sulfamethoxazole (daily prophylactic antibiotics).
   - Palivizumab (passive immunization against the RS virus, a monthly intramuscular application during the RS virus season) available for *all* young children with Down syndrome, not just those with a congenital heart defect.
   - Influenza A vaccination (yearly administration to prevent influenza A, which may set off a severe clinical course in children with Down syndrome; possibly more than one vaccination per year).

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