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Broers, C.J.M.

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Chapter 1

Introduction

Introduction

Down syndrome (DS) or trisomy 21 was first described in 1866 by Sir Langdon Down.¹ In 1959, Jerome Le Jeune discovered the cause of DS: the presence of an extra chromosome in the G group, which was later confirmed to be chromosome 21 (trisomy 21).² Besides developmental delays, children with DS have an increased incidence of several other medical conditions, such as congenital defects of the heart and gastro-intestinal tract, hypothyroidism, leukaemia, orthopaedic problems and diminished vision and hearing, as well as an increased susceptibility to infections.³⁻⁵

There is a wide variety in the phenotype of children with DS. Individuals with DS feature an extra set of genes on chromosome 21. Several research groups have identified Down syndrome Critical Regions on chromosome 21, which contain major genes responsible for the pathogenesis of DS. However, it is still not completely clear which genes are responsible for which phenotype.⁶⁻¹⁰

Daily practice of medical care for children with DS

In the Department of Pediatrics at the VU University Medical Center, we see many children of all ages with DS in our outpatient Down Center. Three paediatricians specialized in DS take care of approximately 400 children with DS, aged 0–18 years. Depending on their age and medical problems, we see these patients 1–4 times a year for their medical check-ups.

Our contact with DS patients often starts as early as the prenatal period, since gynaecologists or clinical geneticists frequently refer parents expecting a child with DS for a prenatal consultation. These parents want to consult a medical expert on DS, who can give them information about the developmental, emotional, social and medical problems their child may encounter in the future. Following this consultation, most parents will have more information to aid them in their decision on whether or not to carry on with the pregnancy. It is very important to give future parents information that covers the broad spectrum of medical issues in DS. Physicians must do this in a professional manner, avoiding personal opinions about DS children and taking account of the specific needs of the parents. The most difficult aspect of the counselling is that the information given is general. It is simply not possible to predict specifically which medical problems *that couple's child* will encounter in the future. Fortunately, a great deal of clinical research has already been conducted and published on DS, including extensive national and international medical guidelines that are

very helpful in these parental counselling sessions.^{3,11-14} In addition, the Dutch DS foundation (Stichting Down Syndroom), which is a patient organization in the Netherlands, as well as parent groups, can inform and support future parents. Aside from invasive prenatal diagnosis by chorionic villus sampling and amniocentesis, there is now a new option for prenatal diagnosis of DS: a non-invasive prenatal diagnostic test (NIPD test), in which foetal cells that are present in maternal blood, are tested for chromosomal abnormalities such as trisomy 21. NIPD testing is easy, safe and can be performed early in the pregnancy. Unlike prenatal diagnosis by chorionic villus sampling and amniocentesis, the NIPD test can be performed without posing any risk of iatrogenic miscarriage.¹⁵ In the Netherlands there is a low uptake of the DS screening programme during pregnancy, as compared to other countries in Europe.¹⁶ The uptake of prenatal DS screening programmes may be higher in the future because of the availability of NIPD testing.

In our outpatient clinic, we check children with DS for the first time during the neonatal period, together with the paediatric physiotherapist, the paediatric cardiologist (to diagnose, confirm or exclude congenital cardiac defects) and the ophthalmologist (to assess the presence of cataracts). The DS clinical guidelines recommend all kinds of preventive blood tests: for example, blood cell counts, thyroid function testing, and screening of celiac disease. These recommendations make it difficult at times for parents to perceive their child as being otherwise healthy.

It is a challenge for paediatricians to maintain the balance between providing early stage prevention or detection of various medical problems and helping the parents of DS children enjoy an otherwise healthy child. In general, we see that not only the parents, but also the older siblings of patients with DS are present during hospital visits, and that they too are very caring about their siblings. For example, they wait for them outside the laboratory when blood is drawn and comfort them afterwards. Younger siblings can also be a big help in the development of children with DS, as they are playmates and thus stimulate them daily in natural interaction to acquire more skills. The parents often need to get used to the fact that a younger sibling outgrows and develops faster than an older sibling with DS, but they are also grateful to see that these siblings can be a great support for the child with DS, now and in the future.

When DS patients reach the age of 18, it is necessary to plan for future medical care by other specialists, including a general practitioner, an internist and other relevant physicians, such as an otorhinolaryngologist, a rehabilitation specialist, an ophthalmologist, an orthopaedic

surgeon and a cardiologist. AVGs (Arts voor Verstandelijk Gehandicapten, the Dutch acronym for Intellectual Disability Physicians) play a crucial role in the coordination of medical care for adults with DS. These physicians are not only experts on the medical, behavioural and social aspects of Down syndrome, but can also guide patients and their parents through the social and legal issues they encounter when their child becomes an adult. At present, the multidisciplinary collaboration between the paediatrician, internist and AVG is becoming increasingly important in the care services our hospital offers.

Respiratory tract infections: a particular problem in DS children

Children with DS are at risk for respiratory tract infections. The most commonly described infection in the airways is the respiratory syncytial virus infection, which can be life-threatening in this special population.^{4,5} One of the reasons for this group's susceptibility is their altered immune system, which differs in many aspects, including in their innate and adaptive immune responses to infections. Many studies have already been conducted on this topic.

As the paediatricians in our hospital, we have had daily experience in our in- and outpatient clinic with the impaired host defence these patients have against infections. The DS outpatient clinic of the VU University Medical Center offered us the opportunity to study these patients' immunological system in greater depth. Fortunately, many patients, siblings and their parents agreed to participate in our studies. Our aim was to elucidate various aspects of these patients' innate and adaptive immunity, and ultimately, to develop preventive strategies to reduce the occurrence of respiratory tract infections in this special population.

Outline of this thesis

This thesis focuses on respiratory tract infections in children with DS as related to alterations in their innate and adaptive immunity.

Chapter 1 contains a short general introduction. **Chapter 2** presents a review of all types of immunological alterations in children with DS, possibly related to their enhanced susceptibility to respiratory tract infections. The next two chapters describe alterations in the innate immunity of 61 children with DS, as compared to 57 of their age-matched, healthy siblings. **Chapter 3** outlines an ex-vivo experiment of whole blood stimulation with heat-killed *S. pneumoniae* and lipopolysaccharide in children with DS. **Chapter 4** follows this

up with an ex-vivo experiment of whole blood stimulation with live influenza A virus in the same group of children with DS. **Chapter 5** examines alterations in adaptive immunity as related to the frequency of lower respiratory tract infections in this group. **Chapter 6** describes the frequency of otitis media, ear, nose and throat surgery and hearing loss in a group of 204 children with DS. **Chapter 7** concludes this thesis with a general discussion, a graphical abstract and future perspectives.

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