Consequences of Down syndrome for patient and family

Weijerman, M.E.

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Michel Weijerman

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Consequences of Down syndrome for patient and family

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Contents

1

Introduction

INTRODUCTION

Down syndrome (DS) is the most common genetic condition, associated with intellectual disability, an increased risk of concomitant congenital defects, and organic disorders. Despite these risk factors, morbidity estimates of DS life expectancy suggest an increase in near future (1).

It was not until the 19th century that DS was recognized as a distinct entity. Escorel described the appearance of a child with DS in 1838. Later in 1866 John Langdon Down published "Observations on an Ethnic Classification of Idiots", and used the name mongolism because of the facial resemblances to East Asian people (2-5). Lejeune, Turpin and Gautier found the third chromosome 21 in patients with DS in 1959. From this turning point forward, the most important question arose concerning the role of the extra chromosome 21 in relation to the phenotype of DS.

To understand DS, it is crucial both to understand the genomic content of chromosome 21 and how the expression levels of these genes are altered by the presence of this third copy. In addition, DS is also associated with phenotypes that vary: not one child with DS is the same as the other. Not until the last years new observations have led to the identification of the long arm of chromosome 21 as the responsible region for the DS phenotype, the DS critical region (DSCR) (2). Chromosome 21 is the smallest chromosome, which may explain the presumed durability of this syndrome over the evolution (2). At this moment more than 450 genes have been identified on chromosome 21, and genes have been identified specifically related to the DSCR (2, 3, 5).

OUTLINE OF THIS THESIS

In the meantime, the outcome of medical aspects, like congenital heart defects (CHD) and gastrointestinal anomalies and DS mortality, has improved. **Chapter 2** gives an overview of the most important medical issues related to the care of children with DS, based on the relevant literature currently available. In **Chapter 3** the prevalence of DS in the Netherlands in 2003 is described, as well as the trend and factors of influence. The first year mortality is analyzed and compared with the past and general population. **Chapter 4** describes celiac disease, one of the specific DS associated gastrointestinal diseases. Prevalence, new diagnostic procedures and its impact on potential preventive policies are discussed in **Chapter 4** and **Chapter 8**, respectively.

CHDs have had a vast impact on morbidity and mortality in DS over the past decades. **Chapter 5** describes the CHDs in children with DS in the Netherlands during the period

2003-2006. The prevalence of the CHDs, the phenomena of the persistent pulmonary hypertension of the neonate with Down syndrome, and the possible relation with neonatal factors were studied.

Respiratory morbidity has an enormous impact in children with DS. **Chapter 6** describes wheeze and its pathophysiologic background and the role of asthma and atopic disease in children with DS.

The current focus should be on how children with DS and their families function and what is needed in respect to their well-being. In **Chapter 7** the relation between medical conditions and the impact on the child in terms of quality of life is described.

In the discussion section (**Chapter 8**) major aspects concerning DS within the scope of future needs and policies are discussed.

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2

Clinical practice
The care of children with Down syndrome

Michel E. Weijerman
J. Peter de Winter

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ABSTRACT

Down syndrome (DS) is one of the most common chromosomal abnormalities. Because of medical advances and improvements in overall medical care, the median survival of individuals with DS has increased considerably. This longer life expectancy requires giving the necessary care to the individual with DS over their total longer lifespan. DS medical guidelines are designed for the optimal care of the child in whom a diagnosis of DS has been confirmed. We present an overview of the most important issues related to children with DS based on the most relevant literature currently available.

INTRODUCTION

Down syndrome (DS) is the most common chromosomal malformation in newborns. In Europe, DS accounts for 8% of all registered cases of congenital anomalies. Throughout the world, the overall prevalence of DS is 10 per 10,000 live births, although in recent years this figure has been increasing. To a large extent, the prevalence of DS depends on several socio-cultural variables. In countries where abortion is illegal such as Ireland and the United Arab Emirates, its prevalence is higher. Conversely, in France, DS prevalence is low, and this is probably due to a high percentage of DS pregnancy terminations.[6,21,33] In The Netherlands, the most recent measure of DS prevalence was 16 per 10,000 live births.[33] In the United Kingdom, the prevalence of pregnancies affected by DS has increased significantly, but there has been no overall change in the live birth prevalence of DS. Increasing maternal age and improved survival rates for infants with Down syndrome have outweighed the effects of prenatal diagnosis followed by the termination of pregnancy and a declining general birth rate.[6,14,24,33,36]

DS is characterized by several dysmorphic features and delayed psychomotor development. Children with DS also have an increased risk of concomitant congenital defects and organic disorders such as congenital heart and gastrointestinal defects, celiac disease and hypothyroidism.[21] The median age at death of individuals with DS has risen significantly in the US, from 25 years in 1983 to 49 years in 1997. Congenital heart defects (CHD) and respiratory infections are the most frequently reported medical disorders on death certificates for individuals with DS.[38] Standardized mortality odds ratios (SMORs) in DS were low for malignancies except for leukaemia and testicular cancer, which were seen more often in individuals with DS.[21,39] Recent decades have seen a substantial increase in the life expectancy of children with DS. In The Netherlands, the infant mortality rate in children with DS dropped from 7.07% in 1992 to 4% in 2003 (this is in contrast with the 0.48% infant mortality of the reference population in The Netherlands in 2003).[33] The fall in DS mortality was mainly related to the successful early surgical treatment of CHD and to the improved treatment of congenital anomalies of the gastrointestinal tract.[33] The life expectancy of children with DS is primarily dependent on the risk of mortality in the first year of life. While modern medical care has reduced the mortality rate to more acceptable values, both morbidity and mortality could be further reduced. In this respect, respiratory infections and neonatal problems are the most important issues to be solved.

Since children with DS now have an improved life expectancy, the total population of individuals with DS is expected to grow substantially. Preventive health care programmes for these children will contribute to the improvement of their overall outcome and quality of life; therefore, it is very important to keep the medical guidelines updated.[11,21]

Newborn assessment

The characteristics of DS and specific clinical signs at birth can guide the decision to perform karyotype testing for the confirmation of a DS diagnosis (**Table 2.1**, **Figures 2.1**, **2.2**).[20,30] Hypotonia is the most striking characteristic, but others include a "Simian fold" (**Figure 2.3**), drinking problems, signs of a CHD, a congenital defect of the gastrointestinal tract or cataract. It will take several days before the first results of the karyotyping can confirm a clinical suspicion of DS.

Table 2.1 Characteristics of Down syndrome and specific clinical signs at birth

Neonatal signs of Down syndrome[20,30]	
Most reliable and discriminative signs	Small ears Wide space in between the 1st and 2nd toe ("Sandal gap") Small internipple distance Brushfield spots Nuchal skin fold
Reliable and discriminative signs	Brachycephaly Hypotonia Flat face Upward slant of the eye split Transverse line in the palm of the hand ("Simian fold")
Age-dependent signs	Epicanthic fold
Difficult to differentiate	Low, flat nose bridge Small mouth

Figure 2.1 A 4-year-old boy with Down syndrome.

Initial postnatal support

The parents or caretakers of a child for whom a diagnosis of DS is being considered or has been confirmed should be informed in a supportive, positive, caring and honest manner.[26] Because parents prefer to receive an accurate and correct diagnosis, the information available to both the paediatrician and the parents should be up-to-date. The conversation must take place with both parents in a quiet setting as soon as the diagnosis of DS is suspected, in the presence of a paediatrician, an obstetrician and the child with DS. The timing of the disclosure of specific DS-related problems must be balanced with respect for the opportunity for parents to welcome their child (**Table 2.2**).[19,26]

Cardiovascular disorders

The prevalence of CHD in neonates with DS is about 44–58% worldwide. Atrioventricular septal defect and ventricular septal defect are the most common forms of CHD, constituting up to 54% for ASD and to 33% for VSD, of all CHDs in children with DS.[31,33] A normal neonatal examination in children with DS does not exclude a serious CHD. Because of the high incidence of significant CHD in children with Down syndrome, early recognition of CHD is necessary as it can lead to the optimal management of the defect and can sometimes prevent the development of pulmonary hypertension. The surgical correction of significant defects usually takes place at the age of 2–4 months, though it is sometimes performed earlier (e.g. in cases of Tetralogy of Fallot). An elevated incidence (5.2–13.7%) of persistent pulmonary hypertension of the neonate (PPHN) with DS has recently been established,

Table 2.2 Prevalence of medical problems in children with Down syndrome

	Prevalence (%)	References
Congenital heart defects	44–58	34
Vision disorders	38–80	21, 27
Hearing disorders	38–78	21
Obstructive sleep apnoea syndrome	57	25
Wheezing airway disorders	30–36	4
Congenital defects of gastrointestinal tract	4–10	9
Coeliac disease	5–7	37
Obesity	30–35	30
Transient myeloproliferative disorder	10	39
Thyroid disorders	28–40	15, 28
Atlanto-axial instability	10–30	12
Urinary tract anomalies	3.2	16
Skin problems	1.9–39.2	18, 23
Behaviour problems	18–38	15, 21

and there should be a specific focus on this condition after birth.[35] Early assessment of the cardiac condition of neonates with DS should always be performed by echocardiography in the first month of life.[8,21,35]

Vision disorders

Good vision is very important to the development of a child, especially a child with developmental problems such as those associated with DS. More than half of children with DS have ocular abnormalities. In addition to ocular features related to DS such as epicanthal folds, narrowed or slanted palpebral fissures (the mongoloid slant) and Brushfield spots (38–85%) (**Figure 2.4**), these vision disorders include strabismus (20–47%), nystagmus (11–29%), congenital cataract (4–7%), acquired cataract (3–15%), blepharitis (7–41%), refractive errors (43–70%) and glaucoma (0.7%). Keratoconus is rare in childhood but develops later in life in individuals with DS.[27,36] Visual screening is essential for detecting defects that can be treated. An early start is especially important in finding congenital cataracts.

Ear, nose and throat disorders

Hearing impairment and otologic problems are prevalent in children with DS, and these problems correlate substantially with developmental problems. Midface hypoplasia is common in children with DS and consists of abnormalities of the nasopharynx, abnormal Eustachian tube anatomy, abnormal tooth development and agenesis of the teeth. These mid-face problems, together with hypotonia and macroglossia (children with DS have a relatively large tongue compared to the oral cavity), are responsible for chronic middle ear disease and chronic rhinorrhoea.

Allergy does not play an important role as a cause of chronic rhinitis in children with DS.[17] On the other hand, a variety of immune disorders makes them prone to upper airway infections.[4] Even mild hearing loss can influence educational, language and emotional developments, and as a result, it can affect a child's articulation skills. Regular assessment of the hearing function is very important. An active search for and treatment of chronic ear disease in children with DS, started soon after birth, may improve hearing.[15] Apart from hearing problems, children with DS have delayed speech development.[21] Sleep-disordered breathing in children with Down syndrome is seen in half of the children with DS. The most common causes include macroglossia, glossoptosis, recurrent enlargement of the adenoid tonsils and enlarged lingual tonsils. There is a poor correlation between parental impressions of sleep problems and polysomnography results. Baseline polysomnography must be considered in children with Down syndrome at 3 to 4 years of age.[8,25]

Figure 2.2 A 2-year-old girl with Down syndrome.

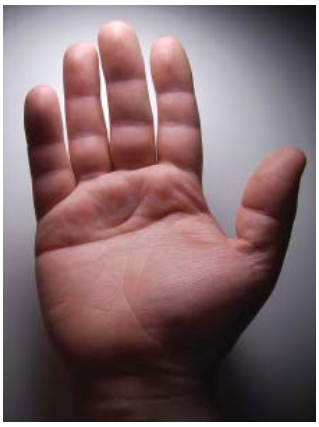

Figure 2.3 Transverse line in the palm of the hand ("Simian fold").

Figure 2.4 Brushfield spots.

Respiratory disorders

Respiratory problems are responsible for the majority of the morbidity and hospital admissions in children with DS. Respiratory syncytial virus (RSV) is seen more frequently and is associated with a greater risk for hospitalization in children with DS. CHD does not influence the admission rate, but children with CHD had longer lengths of hospital stay.[4,13] Recurrent wheeze is very common among children with DS (it is found in up to 36%) and is related to previous RSV infection and to other factors such as tracheamalacia.[3,4] The clinical picture may mimic asthma but is not equivalent to asthma. These respiratory problems can in turn become exacerbated because of the existence of CHD with haemodynamic instability and as a result of hypotonia, both known characteristics of DS. Other causal factors include airway anomalies like tracheolaryngomalacia, pulmonary anatomical changes like pulmonary hypoplasia, and subpleural cysts. Subpleural cysts are common in individuals with DS (up to 36%) but are difficult to detect on plain chest films—CT imaging is needed to detect them.[2] Furthermore, an association with abnormal lung growth and lung hypoplasia is found in children with DS.[1] RSV prophylaxis with human monoclonal antibodies in children with DS with CHD is common, but in a child without CHD, the prophylaxis has to be considered because of their risk of the more frequent and serious infections associated with RSV.[3]

Gastrointestinal tract disorders

Congenital defects of the gastrointestinal tract are present in 4–10% of children with DS and play an important role in morbidity during the first year of life. These defects include oesophageal atresia/trachea-oesophageal fistula (0.3–0.8%), pyloric stenosis (0.3%), duodenal stenosis/atresia (1–5%), Hirschsprung disease (1–3%) and anal stenosis/atresia (<1–4%).These defects are more frequent in the DS population, as much as 25–30% of all cases of duodenal defects are in children with DS.[9] Coeliac disease (CD) is another DS-specific disorder and is seen in 5–7% of children with DS, a rate that is ten times higher than in the normal population.[38] Screening for early detection of CD in the DS population, with the aim of starting treatment and preventing complications from untreated CD such as failure to thrive, anaemia, osteoporosis and malignancy, seems to be justified. For CD screening in children with DS, we recommend human leukocyte antibodies (HLA)-DQ2 and HLA-DQ8 typing in the first year of life with buccal swabs, if available, which have the benefit of avoiding the unpleasant collection of blood. Children who have negative results for HLA-DQ2 or DQ8 (approximately 60%) can be excluded from further screening, and parents can be reassured that their child has no risk of CD. The remaining children need to be monitored for CD by using IgA anti-endomysium (EMA) and anti-tissue transglutaminase antibodies (anti-tTGA) beginning at 3 years of age.[15,38]

The prenatal occurrence of an aberrant right subclavian artery (ARSA, arteria lusoria) is substantially increased in patients with DS where it is found in up to 19–36%. ARSA may cause problems with the passage of solid food through the oesophagus and dysphagia. Moreover, impaired oral motor function, gastro-oesophageal reflux or congenital disorders have to be considered as a cause in feeding problems in children with DS.[9,22]

Constipation is a serious problem in children with DS and is mainly a consequence of the hypotonia; however, in serious cases, Hirschprung disease must be excluded.[8]

Breastfeeding should be promoted not only because of the psycho-emotional or immunity benefits but particularly because breastfeeding has specific advantages for children with DS in terms of stimulating the development of the oral motor system.[33] However, because of their impaired oral motor function, children with DS can have problems with drinking, swallowing and chewing.

Overweight and overnutrition deserve serious attention in children with DS.[21]

Haemato-oncological and immunological disorders

Newborns with DS may have thrombocytopenia (up to 66%) and polycythaemia (up to 33%).[39] The first must be differentiated from pre-leukaemia while the latter may be symptomatic and may cause hypoglycemia or respiratory problems. Children with DS have an increased risk of developing both acute myeloid as well as lymphoblastic leukaemia. These leukaemias have specific presenting characteristics and underlying biologies. Myeloid leukaemia in children with DS may be preceded by a preleukaemic clone (transient myeloproliferative disorder, TMD), which may disappear spontaneously but may need treatment when symptoms are severe. TMD presents in 10% of children with DS. Twenty percent of children with transient leukaemia subsequently develop myeloid leukaemia, usually with an onset before the age of 5.[39] Children with DS have lowered T- and B-lymphocyte counts and functions which may explain part of their susceptibility to infections. On the other hand, there is a lower allergy risk in children with DS.[4,17,18,23,39] There is no specific clinical picture in relation to disturbances of the immune system, which means that screening is not useful.

Endocrine disorders

In neonates with DS, the Gaussian distribution of thyroxin and TSH values are shifted to the left, and there may be a DS-specific thyroid dysregulation. Thyroxin has been given to newborns during the first 24 months, and although shortterm follow-up showed some

benefit to development and growth, there is no data available on the long-term benefit of treating these children with thyroxin.[10,28,29] Therefore, this treatment is not commonly used.

Thyroid disorders have been reported in up to 28–40% of children with DS, and they increase in frequency, up to 54%, as the children age.[10,15,28] Thyroid abnormalities in children with DS range from congenital hypothyroidism (1.8–3.6%) to primary hypothyroidism, autoimmune (Hashimoto) thyreoiditis (0.3–1.4%) and compensated hypothyroidism (25.3–32.9%). In addition, hyperthyroidism (Graves' disease) (0–2%) occurs in children with DS as well. Compensated hypothyroidism or isolated raised thyroid stimulating hormone (IR-TSH) is most frequently present in children with DS and is characterized by mildly elevated TSH with normal or low normal free T4; it often has a self-limiting natural history.[10] These thyroid antibodies are the second most frequently present, and when present, they can cause manifest hypo-or hyperthyroidism within 2 years in almost 30%, but these antibodies are as such not primary related to abnormal thyroid function.[10,15,28] Most predictive of the development of hypothyroidism is the presence of both elevated TSH and antibodies, and those children should be tested more frequently than other children with DS.[9] When both are normal in the first decade of life, there is a low probability of hypothyroidism in the second decade.[10] Interestingly, diabetes mellitus develops more frequently (1%) in children with Down syndrome.[21,30]

Children with DS have their own growth pattern and DS-specific growth curves.[7] The follow-up of length and weight in children with DS should be part of the regular medical screening and special attention for the weight is warranted because children with DS are

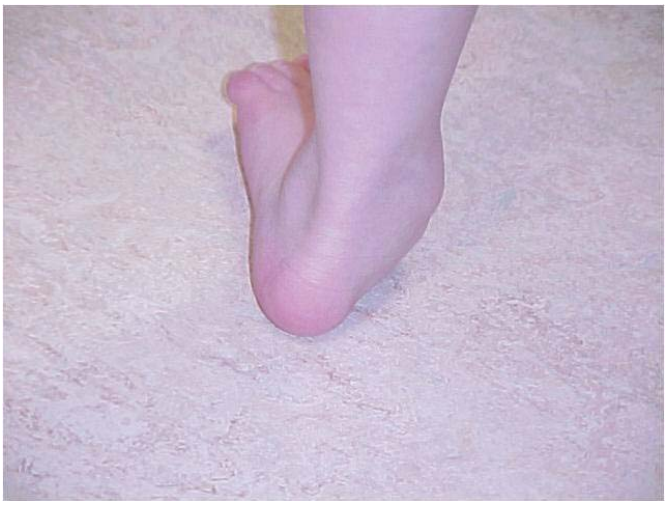

Figure 2.5 Valgus posture of the ankle and pes planus, a typical example of joint laxity.

prone to overweight. Their lack of feeling of satisfaction and their unlimited food intake, as well as their moderate exercise pattern, need special attention.[21]

Orthopaedic disorders

The motoric system of children with DS is characterized by ligamentous laxity, joint hypermobility and hypotonia presenting in a variety of ways.[5,15] Craniocervical instability has been reported in 8% to 63% of children with DS; atlanto-axial instability (AAI) occurs in 10% to 30%. The majority of cases are asymptomatic with symptomatic disease occurring in 1% to 2%, particularly as the result of an accident.[12] There are limitations regarding both obtaining and interpreting and screening X-rays for AAI, and these are not predictive for injury. The performance of yearly neurologic screening is advisable, as is taking extra care when intubation is necessary. Sport activities, including somersaults, can be part of these patients' activities as long as there is a good support.[5,12,21] Individuals with DS have been described as having a specific gait, with external rotation of the hips, knees in flexion and valgus, and externally rotated tibias. In childhood, pes planovalgus is often seen, and in cases where marked pronation of the foot creates problems with stable ambulation, active support is warranted (**Figure 2.5**).[21]

Acquired hip dislocation occurs in up to 30% of children with DS and needs special attention. Patellofemoral instability is estimated to occur in 10–20% of children with DS; slipped capital femoral epiphysis is seen more often in children with DS and has a poor prognosis.[5] Most of these disorders manifest themselves once children with DS start walking, around 2–3 years of age.[5] An arthropathy similar to juvenile rheumatoid arthritis can develop in children with DS but is rare.[5] The delay in motor development in children with DS is more pronounced than the delay in mental development. Delays in motor development appear to be particularly related to the degree of hypotonia, which negatively influences development and leads to problems in postural control and to typically static and symmetrical movement patterns, compensatory movement strategies, and lack of movement variability. Limitations in the functional activities of 5 to 7-year-old children with Down syndrome seem to be more related to the level of motor ability than to the level of performance of mental ability.[32] Special attention to motor development and counselling by a physiotherapist is advised.

DS directed physiotherapy supports the development of the basic gross motor skills properly by challenging the children with DS and giving them confidence in their own physical abilities by making use of the knowledge of the typically movement patterns of DS, furthermore to support parents to start active play and sports.

Urinary tract disorders

Children with DS have significantly more risk of urinary tract anomalies (UTAs) (3.2%). Symptoms may be masked because voiding disturbances and delayed toilet training are usually interpreted as a consequence of delayed psychomotor development. UTAs such as hydronephrosis, hydroureter, renal agenesis and hypospadias must be considered in children with DS. Routine screening by ultrasound is not yet standard, but paediatricians should not overlook this problem.[16]

There are no specific guidelines towards the attitude in delay in daytime and nighttime continence in children with DS; besides the standard treatment, visual instruction is helpful as well as showing them how to do. The advice is to start training at the moment the child can sit properly and understand the items stool, urine and toilet.

Sexual development

In adolescent girls with DS, the onset of puberty is similar to that of other adolescents. In boys with DS, the primary and secondary sexual characteristics and pituitary and testicular hormone concentrations are similar to those in typical adolescents.[21] Females with DS are able to have children, but males with DS have a diminished capacity to reproduce.[21] Education to prevent pregnancies is warranted, specific in children with DS who discuss sexuality open-hearted. In girls, contraception can only be discussed when their mental development enables them to understand the subject.

Furthermore, contraception can be given to prevent pregnancy or when there are problems with the menstrual cycle, for fear of blood or problems with the hygiene.

Unfortunately one must be cautious for sexual abuse in girls with DS.

Dermatologic problems

Dermatologic diseases are often present and are especially troublesome in adolescents.[21] Alopecia areata (2.9–20%), vitiligo (1.9%), seborrhoeic eczema (8–36%), folliculitis (10.3–26%) and syringoma (12.3–39.2%) are more frequently seen in children with DS. Rare but DS-specific problems are elastosis perforans serpiginosa and milia-like idiopathic calcinosis cutis.[18,23] A previously reported high prevalence of atopic dermatitis (AD) in up to 56.5% of children with DS is probably an overestimation, as more recent studies suggest a lower prevalence of 1.4–3%. This could be the result of new and different diagnostic criteria for AD. This observation also notes a lower allergy risk in children with DS, which is in concordance with the studies on allergic rhinitis.[17,18,23]

Neuro-behavioural disorders

Most children with DS function in the low range of typical development, and their intelligence quotient decreases in the first decade of life. In adolescence, cognitive function may reach a plateau that persists in adulthood. Mental development shows a deceleration between the ages of 6 months and 2 years.[32] IQ values vary, usually ranging from 35 to 70, indicating mild to moderate mental impairment; severe mental impairment is only occasionally seen in children with DS.[8] Counterproductive behaviour and avoidance tactics can impede learning, and language production is often substantially impaired. Delayed verbal short-term memory and expressive language indicate the need for a special approach to teaching these children to speak (for example, learning to speak by first learning to read).[15,21] Furthermore, impaired oral motor function can influence articulation.

Children with DS have more pronounced neurobehavioural and psychiatric problems, found in 18% to 38%. The most frequent problems are disruptive behaviour disorders, such as attention deficit hyperactivity disorder (6.1%), conduct/oppositional disorder (5.4%) or aggressive behaviour (6.5%), and obsessive–compulsive disorders. More than 25% of adults with DS have a psychiatric disorder, most frequently a major depressive disorder (6.1%) or aggressive behaviour (6.1%).[15,21] A diagnosis of autism or autism spectrum disorders in children with DS is found in 7%. This diagnosis is not easily made in children with DS mainly because of the resemblance and overlap of DS-specific behaviours and autism.

Epilepsy is seen in 8% of children with DS, with 40% occurring in infancy and often presenting as infantile spasms. Alzheimer's disease which is associated with DS appears later in life, not in childhood.[21]

Education and school

Early intervention education systems are programmes that can be used from the first months of life and provide tools to stimulate the development of children with DS, especially in the preschool period. Children with DS often begin primary school with extra support; successful outcomes are mainly in the area of social skills as a result of the ability to copy and mirror behaviour. The outcome for adult social independence depends largely on the development of abilities to complete tasks without assistance, the willingness to separate emotionally from parents and access to personal recreational activities.[21]

CONCLUSION AND RECOMMENDATIONS

Children with DS have several DS-specific morbidities and screening programmes are available to support and educate patients and their families. Although the most frequently occurring morbidities are emphasized, a potential drawback is that a child with DS might have rare DS-specific problems, but children with DS can also have the same problems as their healthy peers. Today children with DS have a better life expectancy, which means that the total population of individuals with DS is expected to grow substantially. There should be a focus on probable changes in long-term DS morbidity. Furthermore, we need to address the quality of this longer life span. Our recommendations for regular screening are shown in **Table 2.3**.

Table 2.3 Screening schedule for children with Down syndrome 0–18 years

	Timeline for medical assessment of children with Down syndrome			
	0–3 months	4–12 months	Every year	Note
Genetic counselling	+			Once, after birth
Cardiac Ultrasound	+	+		Follow-up depends on the heart defect
Vision[a]	+	+		Every 3 years
Hearing	+	+	+	
OSAS			+	Polysomnography at 3–4 years
Periodontal			+	Dental agenesis
Constipation	+	+	+	
Coeliac disease	+			Every 3 years TGA, once HLA-DQ2 and 8[b]
Growth/Overweight			+	Specific Downcurves- length/weight
Haematology	+		+	TMD at first, leukaemia mainly first 5 years
Thyroid function		+	+	
Hips/Patellae	+	+	+	
AAI			+	Neurologic screening, care during intubation
Physiotherapy	+	+	+	Most impact in first 4 years
Skin			+	
(Pre)Logopaedic	+	+	+	Until speech is well established

OSAS, Obstructive sleep apnoea syndrome.
[a] Initial check for congenital cataract and later for visual assessment.
[b] HLA-DQ 2and 8 when negative, stop when one or both is positive, anti-tissue transglutaminase antibodies (anti-tTGA) every 3 years.

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3

Prevalence, neonatal characteristics, and first-year mortality of Down syndrome: a national study

Michel E. Weijerman
A. Marceline van Furth
Antonie Vonk Noordegraaf
Jacobus P. van Wouwe
Chantal J.M. Broers
Reinoud J.B.J. Gemke

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ABSTRACT

Objective: To determine the prevalence, neonatal characteristics, and first-year mortality in Down syndrome (DS) among children in the Netherlands.

Study design: The number of DS births registered by the Dutch Paediatric Surveillance Unit (DPSU) in 2003 was compared with total live births (reference population) and perinatal registrations.

Results: The prevalence of DS was 16 per 10,000 live births. Compared with the reference population, the 182 children with trisomy 21 had a gestational age of 38 weeks versus 39.1 weeks ($P < .001$), a birth weight of 3119 g versus 3525 g in males ($P < .001$) and 2901 g versus 3389 g in females ($P < .001$), and mothers with a parity of ≥4.17% versus 5% ($P < .001$) and a mean age of 33.6 years versus 31 years ($P < .001$) and 33% (n = 54) ≥36 years. The mean age of DS diagnosis was 10.2 days in nonhospital deliveries and 1.8 days in hospital deliveries ($P < .001$). Children with DS were less often breast-fed ($P < .05$), and 86% (n = 156) were hospitalized after birth. Neonatal and infant mortality were higher in DS, 1.65% versus 0.36% ($P < .02$) and 4% versus 0.48% ($P < .001$), respectively.

Conclusions: The prevalence of DS in the Netherlands exceeds previously reported levels and is influenced by the mother's age. Neonatal and infant DS mortality have declined, but still exceed those in the reference population.

INTRODUCTION

Down syndrome (DS) is the most common chromosomal malformation among newborns, with an estimated prevalence in the Netherlands of 10 to 14 per 10,000 live births.[1] In Europe as a whole, DS accounts for 8% of all registered cases of congenital anomalies.[1] DS is characterized by delayed psychomotor development. Such children also have an increased risk of concomitant congenital defects and organic disorders, such as congenital heart and gastrointestinal defects, celiac disease, and hypothyroidism.[2]

Recent decades have seen a substantial increase in the life expectancy of children with DS. This has been due mainly to the successful early surgical treatment of congenital heart disease[3-5] and the improved treatment of congenital anomalies of the gastrointestinal tract.[6] Preventive health care programs for these children also have contributed to improved overall outcome and quality of life.[2] It is important to assess potential determinants of morbidity and mortality, which has the potential to provide improved outcomes for children with DS in the future.

The aim of the present study was to obtain data on birth prevalence, the duration and complications of pregnancy, any specific neonatal clinical symptoms that prompted the diagnosis, and the first-year mortality in children with DS.

METHODS

The Dutch Pediatric Surveillance Unit (DPSU) is a voluntary national registry that pediatricians use to report various pediatric disorders, including DS. The DPSU is one of 14 such pediatric surveillance units worldwide (www.inopsu.com).

Our study includes all live births in the period between January 1 and December 31, 2003 who were diagnosed with DS and were reported to the DPSU. For each case reported to the DPSU during this period, a questionnaire was sent to the pediatrician in question. The completed forms were returned to the Down Syndrome Study Group of the VU University Medical Center, Amsterdam, where the data were analyzed. The anonymous questionnaire contained 26 questions relating to demographic and medical variables (eg, aspects of the delivery, Apgar scores, birth weight, term figures, congenital defects, and feeding pattern).

DPSU registration data were compared with data from Statistics Netherlands on all live births in the Netherlands and with perinatal data from the National Dutch Neonatal (LNR) and Obstetric (LVR) Registries. Statistics Netherlands administers a mandatory national data collection system based on birth and death certificates; the LNR and LVR

are both voluntary registries. All of these data relate to live births in 2003.[7-9] Data from the DPSU and the LNR and LVR were matched by initials, date of birth, sex, postal code, birth weight, duration of pregnancy, and mother's age. The prevalence of DS among live births was calculated by the capturerecapture method. Data from the DPSU and the LNR-LVR were also matched.[8,10] The data were analyzed using SPSS (SPSS Inc, Chicago, IL), and Student's *t*-test was used to determine statistical significance ($P < .05$).

RESULTS

After corrections for double-counting, 220 children with a suspected diagnosis of DS were reported to the DPSU in 2003. A total of 199 (90%) of the 220 questionnaires were returned, some incompletely filled out. In 2003, the response rates were 96% for the DPSU, 95% for the LVR, and 100% from university hospitals and 50% from nonuniversity hospitals for the LNR.[8]

Chromosomal analysis confirmed the diagnosis of DS in 193 cases, which were then used for further analyses. Six other cases were found to not be DS (**Figure 3.1**). To estimate the prevalence of DS, we matched the 2003 data from the DPSU and the LNR-LVR. This involved 136 DS children who were included in both the DPSU and the LNR-LVR registries. Another 91 children with DS were recorded only in the LNR-LVR registry, and a further 57children with DS were found only in the DPSU registry. Using the capture-recapture method,[8,10] we were able to infer that 38 children had not been registered by any system at

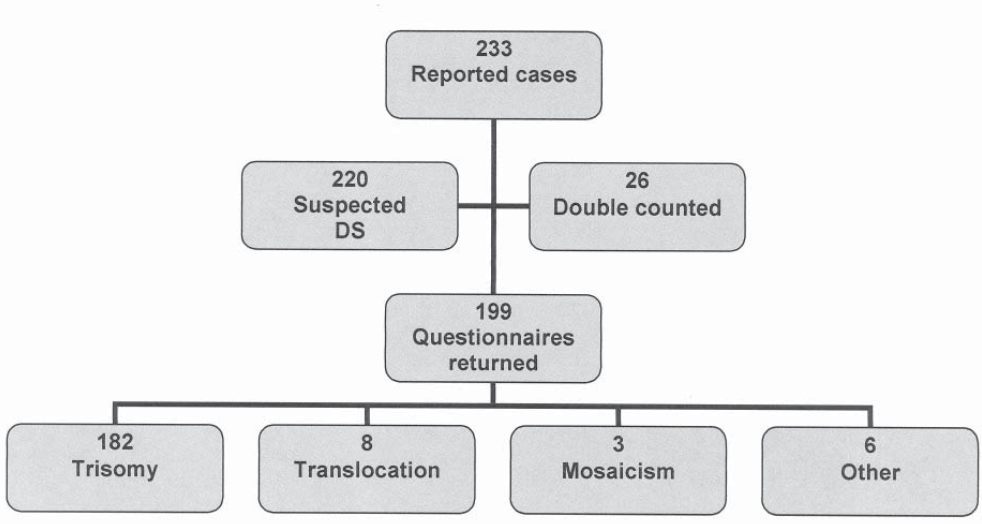

Figure 3.1 Children with DS reported to the DPSU.

all. We calculated that 322 live births with DS occurred in 2003 (95% confidence interval = 303 to 341), corresponding to a calculated DS prevalence of 16 per 10,000 live births (95% confidence interval = 15 to 17) (**Table 3.1**).

The demographic characteristics of the 182 children with trisomy 21 were analyzed and compared with those of the reference population, which comprised all live births in the Netherlands in 2003 (n = 200,297) (**Table 3.2**). We restricted our analysis to the data on children with trisomy 21 because of the homogeneity of this group and of their mothers.

Table 3.1 Calculation of the prevalence of DS by matching the population of the DPSU and the LNR and LVR for 2003 (n = 322)

DS source	DPSU +	DPSU –	Total
LNR–LVR +	136	91	227
LNR–LVR –	57	38 *	95
Total	193	129	322

*Unknown factor, calculated using the capture-recapture method.[8,10]

Table 3.2 Characteristics of trisomy 21 children and the reference population (total live births in 2003 in the Netherlands)

	Trisomy 21	Reference population	*P* value
Birth rate	182	200,297	
Gestational age, weeks (mean)	38	39.1	<.001
Birth-weight, g (mean)			
Male	3119	3525	<.001
Female	2901	3389	<.001
Sex			
Male	54% (n = 99)	51% (n = 102,870)	
Female	46% (n = 83)	48% (n = 97,427)	
Place of birth			
Hospital	70% (n = 126)	67.9% (n = 136,202)	
Home	30% (n = 53)	31.9% (n = 64,095)	
Apgar score ≥6 after 5 minutes	98% (n = 164)	99% (n = 198,294)	
Parity (n = 179)			
1	40% (n = 71)	45.5% (n = 91,120)	
2	33% (n = 60)	37% (n = 73,952)	
3	10% (n = 18)	12.5% (n = 25,299)	
4 or more	17% (n = 30)	5% (n = 9,926)	<.001
Deliveries involving medical intervention	29% (n = 52)	31% (n = 62,092)	

Trisomy 21 numbers varied due to incomplete data collection.

The ethnic background of the DS population (n = 166) reflected that of the reference population, with 80% from the indigenous population and 20% from ethnic minority groups. In terms of the proportions of children born at home and those born in a hospital, there was no significant difference between the group with DS and the reference population. In 149 cases (91%), DS was diagnosed in the first 7 days of life; of these, 129 cases (79%) were diagnosed on the day of birth itself. However, a diagnosis of DS was made at a much earlier stage in infants born in the hospital than in infants born at home (mean postgestational age at diagnosis, 1.8 days vs 10.2 days [$P < .001$]).

In total, 156 (86%) children with DS were admitted to the hospital, generally a few days after birth.

The mean age of the mothers of children with DS was 33.6, versus 31.6 years in the reference population ($P < .001$). Furthermore, 54 (33%) of the mothers of children with DS were age ≥36 years when the index child was born.

We analyzed congenital heart defects (CHDs) in our population, because the severity and treatment of a CHD are very important factors in the outcome of DS. We found CHD in 87 of the 158 children with DS (55%). In terms of the time of DS diagnosis, there was no significant difference between children with a CHD and those without (mean postgestational age, 3.2 days and 2.2 days, respectively). **Table 3.3** lists comorbidities (in addition to CHD) that were reported in the first few weeks of life.

There was a significant difference in the incidence of breast-feeding from birth. Only 48% (n = 83) of the mothers in the DS group breast-fed their child from birth, compared with 78% (n = 156,232) of mothers in the reference population ($P < .05$).

Table 3.3 Comorbidity of children with trisomy 21 (aside from CHD), n = 176

Duodenal atresia	2% (n = 4)
Hirschsprung disease	1% (n = 2)
Congenital diaphragmatic hernia	1% (n = 2)
Hypertrophic pyloric stenosis	1% (n = 2)
Congenital cataract	1% (n = 2)
Hydronephrosis	1% (n = 2)
Transient myelodysplastic disease	0.5% (n = 1)
Thrombocytopenia	0.5% (n = 1)
Total	8% (n = 16)

In 2003, neonatal mortality (ie, mortality in the first 27 days after birth) was 1.65% (n = 3) in children with DS, versus 0.36% (n = 725) in the reference population ($P < .02$). In the same year, 13 children with DS died. The mortality of infants with DS (total mortality in the first year of life) was based on the calculated prevalence of 322 DS live births of 4% (= 13/322%). Infant mortality in the reference population was 0.48% (n = 96) ($P < .001$).

DISCUSSION

Antenatal diagnostics and medical care for children with DS, along with their life expectancy, have improved substantially in recent decades.[2] However, the full implications of these improvements, and of such issues as breastfeeding and hospitalization, are still not fully understood.

The prevalence of DS in the Netherlands in 2003 (16 per 10,000 live births) was much higher than might have been expected based on previous registrations, and higher than suggested in the literature.[1,2,8] Furthermore, the 2003 data for terminated pregnancies reveals a total prevalence of DS (both live births and still births) of 26.8 per 10,000 pregnancies.[9] Eurocat registrations in the northern Netherlands between 1981 and 1990 show much lower DS prevalences of 10.6 per 10,000 live births and 12.8 per 10,000 pregnancies.[1]

Worldwide, the overall prevalence of DS is 10 per 10,000 live births, which seems to have increased in recent years. To a large extent, however, the prevalence of DS depends on sociocultural variables.[1,5,11-13] In countries in which abortion is illegal, such as Ireland[12] and the United Arab Emirates (UAE),[14] prevalence is higher, varying from 17 to 31 per 10,000 live births. Conversely, the prevalence in France is quite low (7.5 DS per 10,000), but this is probably due to a high percentage (77%) of DS pregnancy terminations.[12]

Increasing average maternal age at childbirth is a major reason for the elevated prevalence of DS. In Europe, the proportion of mothers aged 36 and above has increased from 8% to 25% over the past 20 years[12]; we found a proportion of 33%. In some Middle Eastern countries (eg, UAE), 41.6% of mothers were age 36 or older when their child with DS was born.[14] Despite the availability of advanced prenatal screening tests, the affect of maternal age on prevalence must exceed that of DS pregnancy terminations. It should be noted, however, that these tests are not widely used in those countries in which specific policies and sociocultural attitudes against them prevail. Yet, even in the northern Netherlands, where these tests are available for women at increased risk of giving birth to a child with DS, fewer than half (43%) of all eligible pregnant women made use of them.

Furthermore, such tests were not widely used even after they had become available for all pregnant women in the Netherlands, with usage rates of 4.7% in 1991 and in 6.4% in 1996.[12,15] In 1993, based mainly on increases in maternal age over time and in the use of prenatal testing, Cornel et al.[16] predicted that the prevalence of DS in the Netherlands would rise to approximately 17 per 10,000 live births. This figure is in agreement with our results.

In the case of home deliveries, the diagnosis of DS was made a mean of 8.4 days later than in hospital deliveries. This is in agreement with findings previously published by others.[13] It has been suggested that because the delivery of a child with DS is associated with increased risks, delivery should occur in a hospital.[17] However, based on Apgar scores in newborns, we found that the group with DS had no more risk factors than the reference population, and both groups had the same percentages of deliveries involving medical intervention. In addition, there was no difference between these groups in terms of the point in time at which a diagnosis of DS was made in children with or without a CHD. Most children with a CHD are asymptomatic in the first weeks of life.[2] Our study found that DS as such was not the causal factor in neonatal death. The incidence of comorbidity with CHD was only 8% (n = 16), and CHD is mostly asymptomatic immediately after birth. The high percentage of children with DS admitted to a hospital reported in another recent Dutch study (83.2%) confirms our findings (86%).[18] In fact, 16% (n = 26) of these admissions were based purely on the suspicion of a diagnosis of DS, without a specific medical risk factor, and 8.6% (n = 14) were related to maternal disease. In our opinion, there is no reason to admit a child with suspected DS to the hospital, provided that the child has no other medical condition that can necessitate admission.

In our study, only 48% of the children with DS were breast-fed from birth, compared with 78% in the reference population.[7] Because breast-feeding has specific advantages in children with DS in terms of stimulating the development of the oral motor system,[19-23] we suggest that the mothers of such children be encouraged to breast-feed them.

Neonatal mortality in our study was 1.65%. This is lower than most of the levels (1.14% to 4.7%) reported in recent publications[11,17] but is still almost 5 times higher than the level seen in the reference population (0.36%).

The literature indicates that the infant mortality rate is 24.3 times greater in children with DS than in the general population.[24] Over the past decade, however, mortality for infants with DS has fallen from 14.2% to as low as 2.3%.[12] Our study found a infant DS mortality rate of just 4%, which is still more than 8 times greater than that of the reference population (0.48%). Nevertheless, it is better than most values cited in the literature and also better than that found in the northern Netherlands in 1992 (7.07%).[1,7]

CHD is the major cause of infant mortality in DS, particularly during the postneonatal period (70% of cases). In the general population, however, mortality occurs mostly during the neonatal period. In DS, as in the general population, neonatal mortality is caused by such neonatal factors as asphyxia, low birth weight, and prematurity.[7,11,24,25] However, improved techniques for the surgical treatment of CHD, as well as corrections at a younger age, have resulted in a drop in infant mortality and morbidity in DS.[4,6] Our study confirms these findings.

The life expectancy of children with DS depends primarily on the risk of mortality in the first year of life. Although modern medical care has reduced the mortality rate to more acceptable values, both morbidity and mortality can be reduced still further. Respiratory infections and neonatal problems are major issues in this regard.[18]

Children with DS now have a better life expectancy, which, coupled with the worldwide prevalence of DS (which is stable or even increasing slightly), means that the total population of DS individuals is expected to grow substantially. In this respect, future studies should focus on probable changes in long-term DS morbidity. Furthermore, we need to address the quality of this longer life span.

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4

Prospective human leukocyte antigen, endomysium immunoglobulin A antibodies, and transglutaminase antibodies testing for celiac disease in children with Down syndrome

Jeroen Wouters*
Michel E. Weijerman*
A. Marceline van Furth
Marco W.J. Schreurs
J. Bart A. Crusius
B. Mary E. von Blomberg
Laura R. de Baaij
Chantal J.M. Broers
Reinoud J.B.J. Gemke

*The first and second authors contributed equally to this study.

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ABSTRACT

Objective: To assess the effect of a prospective screening strategy for the early diagnosis of celiac disease (CD) in children with Down syndrome (DS).

Study design: Blood samples were taken from 155 children with DS. Buccal swabs were also taken from 9 of these children for determination of human leukocyte antigen (HLA)-DQ2 or HLA-DQ8 positivity. Independently, immunoglobulin A antiendomysium-(EMA) and anti-tissue transglutaminase antibodies (TGA) were tested. An intestinal biopsy was performed to confirm the diagnosis of CD.

Results: Sixty-three children (40.6%) had test results that were positive for HLA-DQ2 or HLA-DQ8. Results of HLA DQ-typing of DNA isolated from blood and buccal swabs were identical. Eight of the children in whom test results were positive for HLA-DQ2/8 also had positive test results for EMA and TGA. CD was confirmed in 7 of these children with an intestinal biopsy, and in 1 child, CD was suggested with improvement on a gluten-free diet.

Conclusions: We found a prevalence of CD in children with DS of 5.2% (10 times higher than the general Dutch population). We recommend HLA-DQ2/8 typing from buccal swabs in the first year of life and initiating serologic screening of children with DS in whom test results are positive for HLA-DQ2 or DQ8 at age 3 years. Early knowledge of negative HLA-DQ2/8 status can reassure most parents that their children do not have a CD risk.

INTRODUCTION

Down syndrome (DS) is the most common chromosomal disorder in newborns. In 2003 the prevalence of DS in the Netherlands was 16 per 10,000 live births.[1] Roizen and Patterson recommended assessing children with DS soon after birth for congenital heart disease, hearing loss, and ophthalmologic problems.[2] Serologic assays are also recommended for common autoimmune diseases such as celiac disease (CD) and hypothyroidism. The prevalence of CD in children with DS (4%-15%) is significantly higher than the general population (0.3%-1.0%).[3-9] In the Netherlands, the prevalence of CD in children with DS was 7%.[10,11]

CD is an autoimmune gastrointestinal disease caused by an intolerance of gluten, derived from wheat, barley, and rye. In children, the presenting symptoms are diarrhea, abdominal distention, growth failure, and fatigue, but the presence of these symptoms has a low predictive value for the diagnosis of CD, especially in children with DS.[5]

CD occurs in genetically predisposed individuals, and it has a strong association with human leukocyte antigen (HLA)-molecules; almost all patients with CD express HLA-DQ2, HLA-DQ8, or both. The HLA-DQ2 and HLA-DQ8 molecules form complexes with tissue transglutaminase (TG2) modified gluten-derived peptides. These complexes trigger CD4 T-cells to respond, resulting in interferon-gamma release in the small intestine, leading to tissue damage and villous atrophy.[12-16] The diagnosis of CD is usually established on the basis of serologic testing, an intestinal biopsy, and the response to a gluten-free diet (GFD).[16]

Csizmadia et al. proposed performing screening for CD in children with DS at 1.5 years of age, by means of HLA-DQ genotyping followed by determination of anti-tissue transglutaminase immunoglobulin A (IgA) antibodies (TGA) and anti-endomysium IgA antibodies (EMA) only in the population that has positive test results for HLA-DQ2, HLA-DQ8, or both.[10] When both the HLA-typing and the serological tests are positive, an intestinal biopsy is performed to confirm the diagnosis of CD. Because of their inferior accuracy, antigliadin antibody tests are no longer recommended.[17]

HLA-DQ genotyping is performed mostly on blood samples obtained with venepuncture.

A non-invasive approach, such as the collection of buccal swabs, is fairly simple and less stressful for children, but has not yet been used for HLA-DQ typing in children with DS.[18]

The main objectives of this study were to assess the effect of the screening strategy for CD in children with DS and to test the feasibility of routine HLA-DQ2 and HLADQ8 sampling with buccal swabs in children with DS.

METHODS

All 155 children who visited the special DS outpatient clinic of the VU University Medical Center, Amsterdam, a mixed secondary and tertiary referral center, from May 2005 to June 2007 were studied. Most children were Dutch Caucasian, but other ethnicities were also included. The ages of the children ranged from 2 months to 19 years (mean age, 7.4 years ± 4.6 SD; male:female, 97:58). Blood samples were taken from all children with DS, and random buccal swabs were collected from 9 of them. HLA-DQ typing was performed, and EMA and TGA antibodies were measured. All the children were checked for IgA deficiency with an enzymelinked immunosorbent assay method using *Escherichia coli* IgA, an alternative test for IgA deficiency. In children < 2 years old, anti-gliadin IgA was measured also. When the serological test (EMA-TGA) results were positive, a small intestinal biopsy was performed to confirm the diagnosis of CD. When pathologic characteristics of CD were found in these children, we assessed the response to a GFD.

HLA-DQ typing

CD is strongly associated with the allelic combination DQA1*05/DQB1*02 (HLA-DQ-2) and to a lesser extent with DQA1*03/DQB1*0302 (HLA-DQ-8). Genomic DNA was isolated from EDTA-anticoagulated blood with a standardized DNAzol-based technique. In 9 children, buccal swabs were collected from each cheek. Subsequently, the swabs were cut off and stored in a 1.5-mL safe-lock tube at –80°C until DNA isolation was performed.

A medium-resolution polymerase chain reaction-single-strand conformation polymorphism/heteroduplex method on a semiautomatic gel electrophoresis system (Pharmacia Phast System) was used for typing the HLA-DQA1 and HLA-DQB1 genotype.[10,19]

Serological tests

The determination of EMA and TGA antibodies was performed from the blood samples. EMA was measured with an indirect immunofluorescence assay with monkey esophagus.[20] The measurements of TGA were performed with a standard enzyme-linked immunosorbent assay procedure.

Intestinal biopsy

Samples were taken from the duodenum to assess small intestinal mucosa.[21] When pathological characteristics of CD (villous atrophy, crypt hyperplasia, increased numbers of intra-epithelial lymphocytes [> 40 IELs/100 enterocytes]) were found, the diagnosis of CD was established.[22]

RESULTS

The results from the screening for CD are presented in **Figure 4.1**. HLA-DQ typing in 1 child, EMA testing in 2 children, and TGA testing in 3 children failed because of technical problems. The 8 patients who were found to have positive test results for EMA and TGA either had a diagnosis of CD confirmed with an intestinal biopsy (n = 7) or were considered very likely to have CD (n = 1) because of improvement both clinically and serologically with GFD.

The prevalence of CD in the DS group was 5.2% (8/155). All 8 children had positive test results for HLADQ2; 6 children were heterozygous for HLA-DQ2, and 2 other children were homozygous. Only 1 of the children was heterozygous for both HLA-DQ8 and HLA-DQ2; the other 5 had negative results for HLA-DQ8.

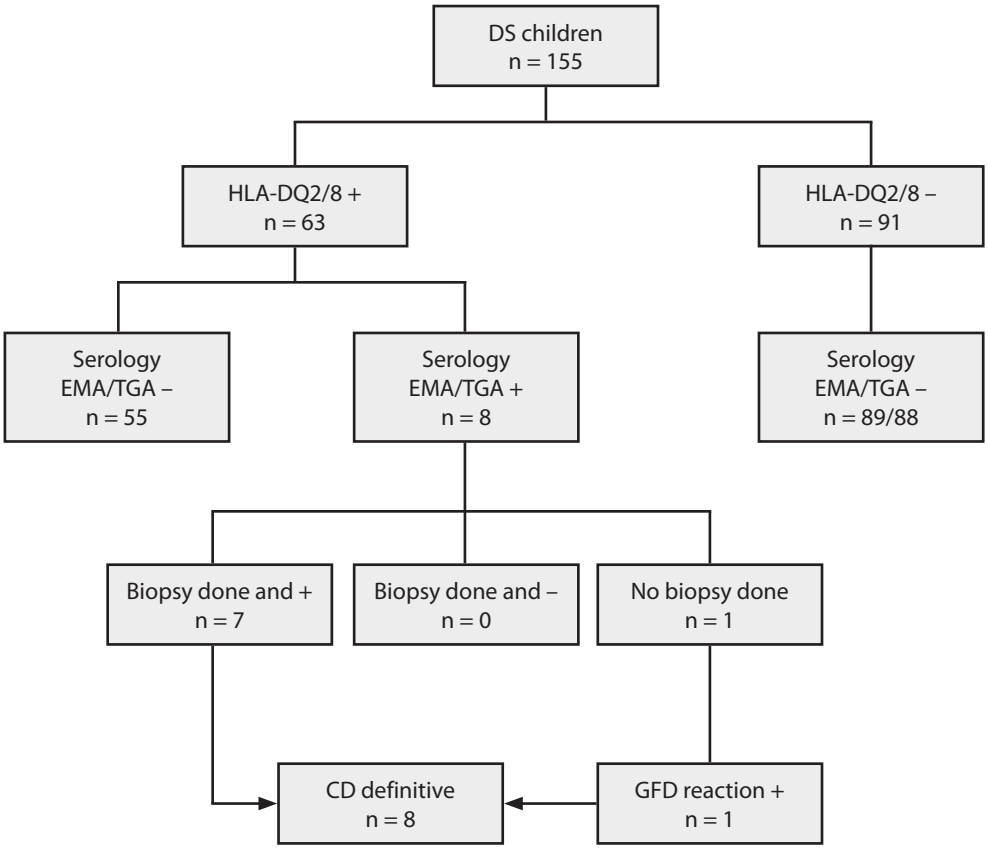

Figure 4.1 Results of screening for CD in children with Down syndrome (DS).

The results of HLA-DQ2/8 genotyping and age distribution of children with DS at the time of screening are presented in **Table 4.1**. There were 31 children < 2 years old; the youngest child was 2 months old. Two of these children with DS had positive test results for anti-gliadin IgA, both of them had negative test results for HLA-DQ2 or HLA-DQ8. There were 6 questionable anti-gliadin IgA measurements. In all 6 of these children, the TGA and EMA results were negative. None of these children underwent an intestinal biopsy.

One of the children who underwent testing was IgA deficient. This child had negative test results for celiac related IgG antibodies. All the other children had positive test results for *E coli* IgA, which excluded IgA deficiency.

The parents of 5 children with DS, in whom CD was diagnosed, clearly noticed an improvement after the children began a GFD (improved stools, disappearance of symptoms, and in 1 child, catch-up growth). Two children with DS did not have any symptoms when CD was diagnosed, but 1 of them had symptoms with the ingestion of gluten after 1 year of GFD. In the other child, no difference was found with or without a GFD.

The buccal swabs obtained from 9 children with DS yield a sufficient amount of DNA with enough purity to perform HLA-DQ typing. This method was as accurate as the HLA-typing on blood samples. The youngest child included in the HLA-DQ-typing with buccal swab was 5 months old.

Table 4.1 Age distribution of the children with Down syndrome at the time of screening (cross-sectional), including the celiac disease cases and the results of HLA-DQ2 and HLA-DQ8 genotyping

Age (years)	Number screened	CD cases	DQ2-homozygous	DQ2-heterozygous	DQ8-homozygous	DQ8-heterozygous
0-2	31	0	0	8	0	9
2-4	28	1	0	8	0	4
4-6	26	1	0	5	0	5
6-8	25	4	2	4	1	4
8-10	15	0	0	2	0	3
10-12	10	0	0	1	0	1
12-14	10	1	0	2	1	2
14-16	4	0	1	0	0	1
16-18	4	1	0	1	0	1
18-20	2	0	0	1	0	0
Total	155	8	3	32	2	30

DISCUSSION

Our study showed a prevalence of CD in children with DS of 5.2% (8/155). This is 10-times higher than in the general Dutch population, although the frequency of the predisposing HLA-DQ2/8 type was comparable with the general Dutch population.[10,23] In 2 earlier studies in the Netherlands, the prevalence of CD in DS was 7%.[10,11] The high prevalence of CD is in agreement with earlier studies and means that screening for CD in the DS population is important.[4-9]

In our study, HLA-typing obtained on buccal swabs from the children with DS fulfilled our expectations and had the benefit of avoiding the unpleasant collection of blood. We propose beginning CD screening in the first year of life, with the HLA-typing on buccal swabs to identify the children with DS who are at risk for CD. This would allow the further selection of a group needing to be screened and a group that can be excluded from further screening because the negative predictive value of the HLA-DQ typing is almost 100%.[16,18,20,24]

By performing this CD screening in the first year of life, more than half the children with DS and their parents can get early reassurance that the child is not at risk for CD.

Furthermore we recommend performing the EMA and TGA test initially at the age of 3 years in HLA-DQ2 or HLA-DQ8 carriers. This advice is based on the results of our study and on the results of the study by Csizmadia et al., in which the youngest children with DS at the time of the CD diagnosis were 3.6 and 3.2 years old.[10] This advice is in agreement with the North American Society for Pediatric Gastroenterology.[17] With this regimen, no CD cases are missed, and unnecessary screening before this age is prevented. Children with DS who have positive test results for HLA-DQ2 or HLA-DQ8 need to be monitored and screened periodically (every 2 or 3 years) with the serological EMA and TGA tests.

In our laboratory setting, the costs of 1 HLA-DQ genotyping are approximately equivalent to 3 serological screenings (tTG IgA and endomysium IgA). Usually, far more than 3 serological screenings will be required per patient in time, indicating that exclusion of the 60% of patients in whom the HLA-DQ2/8 results are negative from screening must be cost effective. Csizmadi also predicted a cost-effectiveness of such a strategy.[10]

HLA-DQ genotyping is very relevant for the diagnosis of CD. In the Northern European countries, HLA-DQ2 has been reported to be present in 90% to 95% of patients with CD.[25-28] The patients with CD who have negative results for HLA-DQ2 almost all have positive results for HLADQ8.[16,29]

Gastrointestinal symptoms are not of predictive value for CD.[5,14]

Although we think a biopsy is needed for confirmation of the diagnosis of CD, in our study we were able to identify the CD cases with HLA-DQ2 or HLA-DQ8 and EMA and TGA measurements.

We studied a large group of children with DS (n = 155) and did a diagnostic work-up (HLA-DQ genotyping, serologic tests EMA/TGA, and an intestinal biopsy in almost all children), but our study also has limitations. We cannot exclude the possibility that, during our 2 years of screening, CD cases were missed. Our study was performed in a single institution, and the children with DS were screened for CD only once. In the HLA-DQ2 or HLA-DQ8 positive group, new CD cases may be discovered in the future.

Early detection of CD in children with DS, with the aim of starting treatment, may prevent complications of untreated CD such as failure to thrive, anemia, osteoporosis, and malignancy and may improve quality of life.[10,16,17] For CD screening in children with DS, we recommend HLA-DQ typing in the first year of life with buccal swabs. Children who have negative results for HLA-DQ2 or DQ8 (an estimated 60%), can be excluded from further screening, and parents can be reassured that their child has no risk for CD. The remaining children need to be monitored for CD by using both EMA and TGA beginning at 3 years of age.

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5

Prevalence of congenital heart defects and persistent pulmonary hypertension of the neonate with Down syndrome

Michel E. Weijerman
A. Marceline van Furth
Maurike D. van der Mooren
Miriam M. van Weissenbruch
Lukas Rammeloo
Chantal J.M. Broers
Reinoud J.B.J. Gemke

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ABSTRACT

The aim of this study was to assess the prevalence of congenital heart defects (CHDs) and persistent pulmonary hypertension of the neonate (PPHN) in children with Down syndrome (DS) and to assess its impact on neonatal factors. It was a prospective study of a birth cohort of children with DS born between 2003 and 2006 registered by the Dutch Paediatric Surveillance Unit (DPSU). A CHD occurred in 43% of 482 children with trisomy 21. Atrioventricular septal defect was found in 54%, ventricular septal defect in 33.3% and patent ductus arteriosus in 5.8%. The incidence of PPHN in DS was 5.2%, which is significantly higher than the general population ($P < .001$). The reported mortality in newborns with DS was overall 3.3% and was still significant higher in children with a CHD versus no CHD (5.8% versus 1.5%) ($P = .008$). The presence of CHD in children with DS had no influence on their birth weight, mean gestational age and Apgar score. In neonates with DS, we found not only a 43% prevalence of CHD, but also a high incidence of PPHN at 5.2%. Early recognition of the cardiac condition of neonates with DS seems justified.

INTRODUCTION

Down syndrome (DS) is the most common autosomal chromosome anomaly, affecting 16 out of every 10,000 live births in the Netherlands.[19] DS is frequently associated with congenital heart defects (CHD). Indeed CHDs are considered to be the most important clinical phenomenon of DS highly relevant to morbidity and decisive in infant mortality.[16] Over recent decades, there has been a substantial increase in the life expectancy of children with DS in general with an improvement in average life expectancy from 12 years in the 1940s to 60 years nowadays.[16] This increase in life expectancyhas mainly been due to the successful early surgical treatment of CHD in children with DS.[5,9,10,16]

Atrio-ventricular septal defect (AVSD), ventricular septal defect (VSD) and atrial septal defect (ASD) are the most common forms of CHD and recent reports have shown that the distribution of CHDs in children with DS may vary with ethnicity.[3,4,7,8,14,15,17,20]

In addition, Shah et al. have recently identified persistent pulmonary hypertension of the neonate (PPHN) in 24 out of 175 children with DS retrospectively; this increased prevalence in children with DS has not previously been identified as a specific problem among children with DS.[13]

In the present study, we describe the prevalence of CHDs in neonates with DS in the Netherlands, determine the incidence of PPHN in this population and analyse the effect of a CHD on other neonatal factors.

PATIENTS AND METHODS

Our study includes all live births of children born between January 1, 2003 and December 31, 2006 who were diagnosed with DS and were reported to the Dutch Paediatric Surveillance Unit (DPSU). The DPSU is a national registry used by paediatricians to report various paediatric disorders, including DS. For each DS case reported to the DPSU, a questionnaire was sent to the attending pediatrician. The completed forms were returned to the Down Syndrome Study Group at the VU University Medical Center, Amsterdam. The method and details of the data collection have already been described earlier, and in 2003 the response rate for the DPSU was 96% and the overall response rate between 2003 and 2006 was 93.3%.[19]

The diagnosis of DS was made in 91% in the first 7 days of life in the Netherlands, and most questionnaires were returned within the first 3 months after birth. In the Netherlands, 20% of the population under the age of 18 is from an ethnic minority background.[19]

Only children with a karyotype analysis (antenatal or postnatal) were included. To ensure the homogeneity of the children with DS, all children with DS due to mosaicism or translocation were excluded. Children with DS for whom information regarding their cardiac status was absent or incomplete were also excluded. The Dutch DS screening program carries out an echocardiogram within the first 3 months of birth. We used the following items in the questionnaire for the analyses: sex, chromosomal analysis, ethnicity, cardiac evaluation, birth weight, gestational age of birth, 5-min Apgar score and the presence of PPHN. The diagnosis of PPHN was based on a clinical assessment and echocardiogram in the first week of life performed by neonatologists or paediatric cardiologists who answered the questionnaires. PPHN is defined, if the pulmonary pressure exceeds the systemic pressure, as being present a right-to-left shunt and is diagnosed by echocardiography. The use of a high percentage of oxygen is needed usually without a reaction on 100% oxygen and a difference in oxygen saturation measured pre-ductal and post-ductal, when a PDA is present.[1, 3,18] Secundum ASD and persistent foramen ovale (PFO) were excluded as a CHD.

Statistical analysis

The binomial test was used to compare the prevalence of CHD and PPHN in children with DS and the Dutch reference population, respectively. We tabulated the frequency of CHD and the combinations of CHDs. Statistical comparisons of birth weight and gestational age for children with DS with and without CHD were made with independent sample t tests. Because of the influence of the gestational age on birth weight, we corrected birth weight for gestational age by using a multiple regression model. We used the Mann–Whitney test to compare nonparametric variables (e.g. Apgar score) and the Chi-square test for paired comparison of properties (e.g. asphyxia, ethnicity and mortality). Statistical analysis was performed with SPSS 16.0 statistical software. A P value of $< .05$ was considered significant.

RESULTS

Study group

The DPSU registered 820 children with DS who were born between January 1, 2003 and December 31, 2006. A total of 630 questionnaires were returned by the DPSU, and of these, 482 included complete data regarding the cardiac status. A CHD was reported in 207 (43%) of the children with trisomy 21, which is significantly higher than the prevalence of CHD in the Dutch reference population (0.62%, $P < .001$) (**Figure 5.1**).[12]

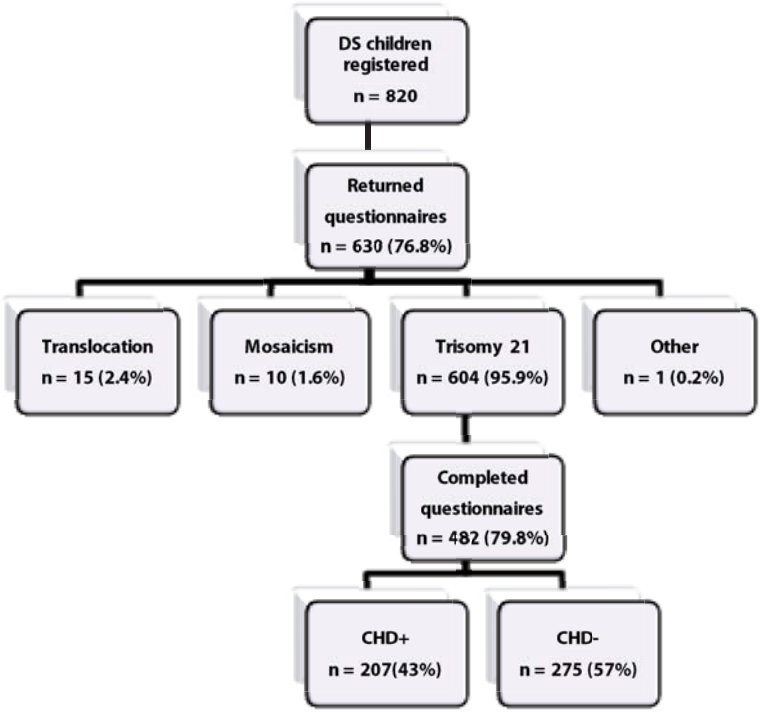

Figure 5.1 Children with Down syndrome (DS) in the Netherlands born in the period January 1, 2003 to December 31, 2006 with and without congenital heart defect (CHD). Asterisk (*) one child had a combination of trisomy 21 and triple X (0.2%).

In 2003, the prevalence in the Netherlands of live and still-born children with DS was 26.8 per 10,000 pregnancies compared with 16 newborns with DS per 10,000 live births; there were no exact data on the prevalence of CHD in these stillborn children with DS.[19]

Congenital heart defects

The data for CHD in children with DS are summarized in **Table 5.1**. In 2.4% (n = 5) of children, the CHD did not match any of the categories mentioned and thus these were thus counted as 'other'. In 28.9% (n = 60) of the children, there were multiple cardiac defects (i.e. a combination of defects).

Table 5.1 Children with Down syndrome and a congenital heart defect (CHD; total n = 207)

Congenital heart defect (CHD)	n	Percent
Single defect	147	71.0
AVSD	92	44.4
VSD	38	18.4
PDA	12	5.8
Other		
Hypoplastic pulmonary arteries	1	0.5
COA	1	0.5
PS	2	1.0
AR	1	0.5
Combination of defects	60	29.0
AVSD + TOF	3	1.5
AVSD + ASD	6	2.9
AVSD + other		
Hypoplastic aortic arch	1	0.5
IAA-b	1	0.5
PS	1	0.5
TOF	8	3.9
VSD + ASD	29	14.0
VSD + overriding AO	2	1.0
ASD + PS	7	3.4
Other		
CAT-II + IAA-a	1	0.5
DAA	1	0.5
Total	207	100.0

ASD, secundum atrial septal defect; AVSD, atrioventricular septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; TOF, Tetralogy of Fallot; IAA-a, interruption of the aortic arch type a; IAA-b, interruption of the aortic arch type b; COA, coarctation of the aorta; PS, pulmonary valve stenosis; AR, aortic regurgitation; CAT-II, common arterial trunk type II; DAA, double aortic arch.

Ethnicity

The ethnic background of children with DS was reported for 404 children and was predominantly Caucasian (77.5%, n = 313). Of these Caucasian children, 127 (40.6%) had a CHD. In 22.5% (n = 91), one or both of the parents came from an ethnic minority group most of which were from a Moroccan, Turkish or Antillean background. Within this ethnic group, 42.9% (n = 39) of the children with DS had a CHD. There were no differences in the distribution of CHDs neither in the ethnic group compared to the Caucasian group nor within the ethnic subgroups. The data on ethnicity were missing for 78 children with DS.

Persistent pulmonary hypertension of the neonate

PPHN was reported in 25 children with DS; an incidence of 5.2%, which is significant, elevated in comparison with the reported 0.1% in the general population ($P < .001$).[18] **Table 5.2** shows the distribution of CHDs in children with DS and PPHN of which 36% (n = 9) of the children had no CHD.

Neonatal variables

The presence or absence of a CHD had no significant relationship with birth weight and gestational age. The mean birth weights of the children with and without a CHD were 2,926 and 3,013 g, respectively (95% CI; −270–87), and the mean gestational age of the children with DS with and without CHD were 38.0 and 38.3 weeks, respectively (95% CI; −0.64–0.16). The median of the Apgar score at 5 min was nine in children with DS both with and without a CHD. Also, the frequency of asphyxia (Apgar score < 6) in children with DS with a CHD did not differ from those without a CHD (1.6% versus 2.8%) ($P = .39$).

Mortality

The reported mortality among the neonates with DS was 16 out of 482 (3.3%). Most of the 16 children with DS died within 30 days of birth (n = 11), one died on day 39 and another on day 318 following birth. The data of the remaining three non-survivors are missing. Among the neonates with DS who died, 12 children had a CHD (12 out of 207 CHD children (5.8%)) and four children had no CHD (4 out of 275 non CHD children, 1.5%). This was a significant difference in mortality among the children with DS with and without a CHD, ($P = .008$). The causes of death in the 12 children with DS and a CHD were as follows: respiratory distress (n = 3, all AVSD), neonatal infection (n = 2, AVSD

Table 5.2 Children with Down syndrome and persistent pulmonary hypertension of the neonate (PPHN) (n = 25) and the distribution of a concomitant congenital heart defect (CHD)

Congenital heart defect (CHD)a	n	Percent
AVSD	7	28
VSD	6	24
VSD + ASD	3	12
No CHD	9	36
Total	25	100

ASD, atrial septal defect; AVSD, atrioventricular septal defect; VSD, ventricular septal defect.

and aortic regurgitation), asphyxia (n = 1, AVSD), post cardiac operation (n = 1, AVSD) and necrotizing enterocolitis (n = 1, VSD). In four children, the cause of death was not documented in the questionnaires (three AVSD and one PDA). The four children without a CHD died as a result of asphyxia, respiratory distress and infection, respectively, and one cause of death was unknown.

DISCUSSION

This is the first large-scall study in the Netherlands regarding CHDs in children with DS. We found a prevalence of CHDs of 43%, which is concordant with the prevalence presented in the literature of 44–58%,[3,4,7,8,14,15,17,20] AVSD (54%) was the most commonly occurring CHD in children with DS in our study. In our study, early diagnostic echocardiography was performed. Secundum ASD and persistent foramen ovale (PFO) were excluded as a CHD because a small secundum ASD is sometimes difficult to differentiate from a persistent foramen ovale, and the study design did not include follow-up to provide sufficient clarity about ASD versus PFO.[9,16] This could have caused an underestimation of the prevalence of CHD in our study. The early diagnostic procedure was used to make an early assessment of cardiac anatomy and in case of a significant defect to perform early intervention and to prevent pulmonary arterial hypertension in defects with a left to right shunt.

The inclusion of various cardiac defects and the use of different terminology in studies with children with DS made it difficult to compare these studies with our results. For instance, Stoll et al. did not report ASD as a CHD as well, which may explain why PDA is one of the three most prevalent defects in their study.[7,10,14,17] In our study, there was no significant difference in the distribution of CHD according to ethnicity, as the subgroups were too small.

Freeman et al. reported in their study in the United States of America that black infants with DS had an AVSD more frequently than whites and that Hispanic infants with DS had an AVSD less frequently than whites.[4] In Chinese children with DS and a CHD, VSD was seen in 38% and AVSD in 25%.[7] AVSDs accounted for only 9% of the CHDs in Mexican children with DS, while ASD, VSD, and PDA were most common. This study however began at the age 13, so the mortality prior to the age of 13 may explain their distribution of CHDs.[3]

Another relevant phenomenon which, to our knowledge, had not previously been appreciated and as such was not included in DS guidelines[2,6] was the significantly increased incidence of PPHN in neonates with DS (5.2%) we found in our study. This corresponds

with Cua et al. who estimated the incidence of idiopathic PPHN in neonates with DS between 1.2% and 6.6%, which is much higher than the reported overall incidence of 0.1% in the general population.[1] In our study, only seven children (28%) had an AVSD, and in these children, we cannot exclude a relationship with the development of PPHN and nine (36%) children with DS and PPHN did not have a CHD. In addition Shah et al. found no serious structural heart defect in 70% of children with DS and PPHN.[13] PPHN should be distinguished from another type of pulmonary hypertension, originating from a cardiac defect that permits left-to-right shunting and requires some period of time to be clinically detected. The newborn children with DS, who develop PPHN, are by contrast symptomatic just after birth.[1,13,18]

Wren et al. found no clinical signs in the first weeks in some children with DS, with major cardiac malformations and associated pulmonary hypertension, even in some who progressed to irreversible pulmonary vascular disease.[21] A normal neonatal examination in children with DS does not therefore exclude a serious CHD.[11] This corresponds with our findings and emphasizes the importance of an early echocardiography of neonates with DS to detect any CHD and to determine the possible risk of developing pulmonary hypertension, as supported by the DS health care guidelines published by the American Academy of Pediatrics and the Down Syndrome Medical Interest Group of the United Kingdom and Ireland.[2,6] Because of the high incidence of a significant CHD in children with Down syndrome, the early recognition of CHD can lead to the optimal management of the defect. The surgical correction of significant defects usually takes place at the age of 2–4 months, though this happens earlier in certain cases (e.g. TOF).[9,10]

In our study, basic neonatal characteristics, Apgar scores, birth weight and gestational age were not different in children with DS with and without CHD. This is in concords with Frid et al. who analysed the influence of CHD on these neonatal issues in 304 neonates with DS and also found no difference between those with and without CHD.[5]

In the past decade, research has shown that neonatal mortality in DS appears to be becoming less dependent on CHDs and more often caused by neonatal pathology such as asphyxia, low birth weight and prematurity, as in the general population.[5,19] With regard to mortality, we should emphasize that with the exception of one child who died following a cardiac operation, the presence of a CHD was not responsible for reported mortality in children with DS in our recent study.

Our study has several limitations. Because of its retrospective design, we used data from questionnaires completed by paediatricians and have no on follow-up data. Furthermore, there was a sample bias since we could not use the data of all 820 children with DS who

were registered by the DPSU, 630 (76.8%) questionnaires were returned and not all questionnaires relating to children with trisomy 21 had complete data on cardiac status. On the other hand, the fall out cases were distributed between both the CHD and non-CHD children with DS.

Though the definition of PPHN was not specifically defined, diagnosis was based on the clinical assessment and an echocardiogram performed by the neonatologists and pediatric cardiologists who answered the questionnaires. It was impossible to draw a definitive conclusion on the exact role of the AVSD in the seven children with an AVSD in relation to the cause of the pulmonary hypertension; nevertheless, there were at least 18 other children (3.7% of total) with PPHN that was not related to a CHD, which is still a high level.

In conclusion, we have demonstrated a 43% prevalence of CHD in neonates with DS and a significantly increased and elevated incidence of PPHN in neonates with DS (5.2%) compared to the general population. Early recognizing the cardiac condition of neonates with DS seems justified. CHDs had no relationship with neonatal factors such as gestational age, Apgar score and birth weight of children with DS.

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6

Recurrent wheeze in children with Down syndrome: is it asthma?

Michel E. Weijerman
Paul L.P. Brand
Marceline A. van Furth
Chantal J.M. Broers
Reinoud J.B.J. Gemke

Acta Pædiatrica, 2011; 100: e194-e197

ABSTRACT

Aim: To compare the prevalence of current wheeze in children with Down syndrome (DS), their siblings, and nonrelated population controls.

Methods: This was a case–control study in which the International Study of Asthma and Allergy in Childhood questionnaire for respiratory symptoms was completed by parents for 130 children with DS, 167 of their siblings, and for 119 age- and sex-matched control subjects from the general population.

Results: Both wheeze ever and wheeze during the last 12 months was more commonly reported in DS than in their siblings or controls. The relative risk (RR) of current wheeze in DS was 2.8 (95% CI, 1.42–5.51) compared with siblings, and 2.75 (95% CI, 1.28–5.88) compared with controls. A doctor's diagnosis of asthma was found in 3.1% in children with DS, in 4.2% in siblings and in 6.7% in controls. During 4-years follow-up, the diagnosis of asthma could not be confirmed in the 24 DS children with current wheeze, and atopy was found in none of them.

Conclusion: Wheeze is common in children with DS. This is likely to be related to the factors specific for DS and probably unrelated to asthma.

INTRODUCTION

Respiratory problems occur frequently in children with Down syndrome (DS).[1,2] In addition to congenital malformations such as subpleural lung cysts, pulmonary hypoplasia and abnormalities of the tracheobronchial tree, respiratory disorders in DS include sleep-disordered breathing, severe lower respiratory tract infections and pulmonary hypertension.[1-4] Recurrent wheezing has been reported in more than one-third of children with DS.[5,6] Many of these wheezy children with DS are diagnosed as having asthma and treated accordingly.[5] Treatment with anti-asthmatic medication in these children, however, is usually unsuccessful.[2] This suggests that the underlying mechanisms of wheezing in DS are different from those in asthma.

Numerous factors have been suggested to play a role in the pathophysiology of recurrent wheeze in DS, including tracheobronchomalacia, muscle hypotonia, compression of the intrathoracic airways by congenital heart defects and upper airway obstruction.[1-3] In the few studies that specifically examined recurrent wheezing in DS, traditional risk factors for asthma did not seem to play a role; for example, no association of wheezing in DS was found with previous hospitalization for respiratory syncytial virus bronchiolitis.[6] Similarly, the prevalence of positive skin prick test results in children with DS was much lower than in controls.[7]

The aim of this study was to compare the prevalence and risk factors of recurrent wheeze in children with DS to two groups of controls: a group of children from the general population and siblings of patients with DS. The latter group was included because they share the genetic and environmental background with the DS group.

METHODS

Patients

This was a case–control study conducted in the outpatient clinic of the VU University Medical Centre (VUmc) in Amsterdam, the Netherlands. The VUmc has a dedicated outpatient clinic for children with DS, which accepts children with DS referred by parents themselves, general practitioners and paediatricians from within and outside the hospital. The national Down syndrome foundation encourages parents of children with DS to visit a dedicated DS outpatient clinic regularly for medical check-up and advice.

In 2004, parents of all children (0–18 years) attending the VUmc DS outpatient clinic were sent the International Study of Asthma and Allergy in Childhood (ISAAC) questionnaire.[8]

They were asked to complete this questionnaire for their child with DS and for the sibling whose age was closest to the child with DS. We also collected data on asthma symptoms from abbreviated ISAAC questionnaires in a randomly chosen age- and sex-matched control group from schools and day-care centres throughout the Netherlands. The parents of these eligible control children were approached by mail.

Questionnaire

We used the validated Dutch translation of the ISAAC questionnaire to assess respiratory symptoms and associated risk factors. 'Wheeze ever' was defined as an affirmative answer to the question 'Has your child ever had wheezing or whistling in the chest?', 'current wheeze' as an affirmative answer to the question on wheezing or whistling in the last 12 months. An affirmative answer to the question 'whether asthma had ever been diagnosed in the child' was considered to signify 'doctor's diagnosis of asthma'.

Follow-up

All children with DS whose parents reported current wheeze or doctor's diagnosis of asthma were followed up at the outpatient clinic for patients with DS at the VUmc for at least 4 years, during which specific attention was paid to respiratory symptoms. Parents were asked to present their child when symptomatic, and the attending paediatrician (MW), who also examined all the children at all visits, made or refuted the diagnosis of asthma according to international guidelines.[9] Total serum IgE and the specific inhalant allergen enzyme immune assay (house dust mite, cat and dog dander, grass and tree pollen) were measured.

Ethical considerations

The study was reviewed and approved by the institutional review board of the Vumc under Dutch law, a study involving questionnaires sent to healthy adults (the parents of the children involved) does not require formal assessment and approval. Both the clinical examinations and the laboratory tests were performed as part of our standardized clinical routine of DS preventive health care programme.[1]

Statistical analysis

Differences between proportions were analysed using chisquared tests; differences between means with Student's t-test for independent samples. Analyses were carried out with SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The parents of 173 children (0–18 years) with DS who visited the DS outpatient clinic at the VUmc participated. Thirty-three of these (19.1%) declined to participate; 10 others (5.8%) failed to return a completed questionnaire. A total of 130 completed ISAAC questionnaires from children with DS could be analysed (response rate 75.1%). The age and sex of the DS children with completed questionnaires did not differ from those of the root population of 173 children with DS. Most children with DS (118 = 90.8%) were Caucasian. Demographic characteristics of the children with DS, their siblings and controls are presented in **Table 6.1** together with data on wheeze and diagnosis of asthma. Children with DS had significantly more parent-reported current wheeze than siblings (P = .003) and controls (P = .01), particularly in children below 4 years of age (**Table 6.1**). In contrast, more control children had been diagnosed with asthma (6.7%) than children with DS (3.1%; P = .04). Nocturnal dry cough outside a common cold was found in 25 (19.2%) of the children with DS.

To examine whether the 24 children with DS and current wheeze had asthma, these patients were followed prospectively for 4 years by a single paediatrician (MW), with special emphasis on respiratory symptoms and signs. Following international guidelines,[9] the diagnosis of asthma could not be confirmed in any of these patients during long-term follow-up. They were prescribed no inhaled corticosteroids or bronchodilators. In 17 of these patients (71%), screening for aeroallergen sensitization was performed; no such sensitization was found. Eleven of the DS patients who reported current wheeze in the original survey (46%) had a congenital heart defect (four atrioventricular septal defect; seven atrial of ventricular septal defect). All these had been corrected surgically when needed, and at the time of the survey, haemodynamically important cardiac defects were no longer present in any of these patients.

The prevalence rates of rhinitis, eczema symptoms and hay fever in the patients with DS and their siblings (these data were not collected in the nonrelated controls) are presented in **Table 6.2**. Rhinitis ever or during the preceding 12 months was significantly more common in children with DS than in their siblings (P < .001). Very few children were diagnosed with hay fever, and this did not differ between children with DS and their siblings (**Table 6.2**). Itchy rash and eczema diagnosis were equally common in the two groups.

DISCUSSION

This study shows that parent-reported current wheezing occurs more frequently in children with DS (18.5%) than in their siblings (6.6%) and in nonrelated controls (6.7%). In addition, children with DS had more persistent rhinitis symptoms than their siblings. Patients with

Table 6.1 Basic characteristics and main results from the children with Down syndrome, their siblings and the control group

	Down syndrome n = 130	%	Siblings n = 167	%	RR (95% CI)*	Control group n = 119	%	RR (95% CI)†
Sex ♂	83	64	82‡	49.1		72	60.5	
Age mean ± SD	6.8 ± 4.1		8.3 ± 4.2			6.8 ± 4.0		
≤ 4 years	49	37.7	35	21		40	33.6	
5–18 years	81	63.3	132	79		79	66.4	
Wheeze								
Ever	50	38.4	26	15.6	2.47 (1.63–3.74)	22	18.5	2.08 (1.35–3.22)
≤ 4 years	20	40.8	3	8.6	4.76 (1.53–14.8)	6	15.0	2.72 (1.21–6.12)
	♂ 14		♂ 2			♂ 3		
5–18 years	30	37	23	17.4	2.12 (1.33–3.4)	16	20.2	1.83 (1.09–3.08)
	♂ 20		♂ 11			♂ 9		
Current	24	18.5	11	6.6	2.8 (1.42–5.51)	8	6.7	2.75 (1.28–5.88)
≤ 4 years	13	26.5	3	8.5	3.10 (0.95–10.0)	3	7.5	3.54 (1.08–11.6)
			♂ 2			♂ 1		
5–18 years	11	13.6	8	6.1	2.24 (0.94–5.34)	5	6.3	2.15 (0.78–5.90)
	♂ 7		♂ 4			♂ 2		
Asthma								
Ever	4	3.1	7	4.2	1.36 (0.41–4.55)§	8	6.7	2.19 (0.68–7.07)¶
≤ 4 years	0	0.0	1	2.8	4.17 (0.18–99.4)§	1	2.5	3.66 (0.15–87.4)¶
			♂ 1			♂ 1		
5–18 years	4	4.9	6	4.5	0.92 (0.27–3.16)§	7	8.9	1.79 (0.55–5.90)¶
	♂ 3		♂ 3			♂ 3		

* RR (Relative Risk, 95% confidence interval, CI) Down syndrome versus siblings.
† RR (Relative Risk, 95% confidence interval, CI) Down syndrome versus the control group.
‡ One unknown 0.6%.
§ RR Asthma: siblings versus Down syndrome.
¶ RR Asthma: control group versus Down syndrome.

Table 6.2 Prevalence of rhinitis, hay fever, rash and eczema in children with Down syndrome and their siblings

	Down syndrome (n = 130)	Siblings of children with Down syndrome (n = 167)	
	n (%)	n (%)	RR (95% CI)
Rhinitis*	52 (40.0)	29 (17.3)	2.30 (1.56–3.41)
Rhinitis during last 12 months	44 (33.8)	24 (14.4)	2.36 (1.51–3.66)
Doctor's diagnosis of hay fever	3 (2.3)	10 (6.0)	0.39 (0.11–1.37)
Itchy rash > 6 months	19 (14.6)	32 (19.2)	0.76 (0.45–1.28)
Doctor's diagnosis of eczema	20 (15.4)	26 (15.6)	0.99 (0.58–1.69)

RR, relative risk; 95% CI, 95% confidence interval.
* Affirmative answer to the question 'has your child ever have a problem with sneezing, or a runny or blocked nose when she/he did not have a cold or flu?'.

DS were less commonly diagnosed with asthma than their siblings or controls, yet a doctor's diagnosis of hay fever was equally uncommon in patients with DS and their siblings. There were no differences in eczema prevalence between children with DS and their siblings.

The results of our study confirm the scanty previous findings that wheeze is a common problem in children with DS.[6] In a cohort of 163 children with DS, prevalences of recurrent wheeze of 30% and 36% were reported in those who had and had not been hospitalized with respiratory syncytial virus bronchiolitis, respectively.[6] No data on doctor's diagnosis of asthma were reported in this study. In a recent nationwide random population sample of 95,454 children in the United States, 32/146 (19.4%) children with DS were diagnosed with asthma,[5] but it was not reported how the diagnosis of asthma was made. We were unable to confirm a diagnosis of asthma (according to international asthma guidelines[9] in any of the DS patients with current wheeze during 4-years follow-up. Diagnosing asthma in children with DS is hampered by the difficulty in performing lung function in these patients. To our knowledge, feasibility and reliability of measuring lung function in children with DS has never been formally studied. In our experience, measuring lung function is not feasible in the majority of patients with DS, not only because of their limited cognitive abilities but also because of the muscle hypotonia and coordination problems.[1,3] Although some lung function techniques only require passive cooperation, the feasibility and reliability of such techniques in DS had been insufficiently documented to allow for robust measurements in the context of our study.

The low prevalence of atopic sensitization in DS in our study is in agreement with the rare occurrence of confirmed asthma and confirms earlier work. Recently, aeroallergen

sensitization was found in 7/39 children with DS (18%) versus in 21/39 controls (54%).[7] The low prevalence of atopy in children with DS suggests that the pathophysiological mechanisms causing wheeze in subjects with DS is different from those in asthma. Conversely, autoimmune disorders such as coeliac disease, hypothyroidism and diabetes mellitus are much more common in DS.[1] This suggests a T-helper 1/2 cell imbalance or regulatory T-cell dysfunction in DS.[10] Indeed, abnormalities in T- and B-cell function and in the innate and adaptive immune systems have been shown in children with DS, but further study is needed to establish the potential immunologic basis of recurrent wheeze in patients with DS.[2,11] A number of other pathophysiological factors should be considered in explaining the high prevalence of wheeze in DS. First, congenital lung abnormalities reducing the elastic recoil of lung parenchyma may reduce intrathoracic airway patency in DS.[2,12] Second, intrathoracic airway malacia has been described in patients with DS, which may not only cause wheeze but may also explain the increased prevalence and severity of respiratory infections in young children with DS.[2,4,12-16] The higher prevalence of wheeze in preschool than in school-aged children with DS in our study supports the notion that airway malacia may be partly responsible for the recurrent wheeze in our cohort. Airway malacia tends to improve with increasing age, while asthma is more likely to persist.[16-18] Although congenital heart disease needs to be considered in young children with DS and respiratory morbidity, it is unlikely to have played a role, because all children in our study were haemodynamically stable.[1,19] Finally, muscle hypotonia and upper airway collapse may contribute to wheeze prevalence and severity in children with DS.[1-3]

Thus, recurrent wheeze in patients with DS appears to be a multifactorial condition. In the absence of evidence of atopy and the high likelihood of other factors contributing to wheeze in DS, we discourage the use of the diagnostic label 'asthma' to describe recurrent wheeze in children with DS.

Our study has several limitations. First, we used the ISAAC questionnaire for 6- to 7-year-old children to assess prevalence of wheeze in children 0–18 years of age. Formally, this questionnaire has not been validated for use in such a broad age range, although the differences of the wheeze questions in ISAAC questionnaires between 6- and 7-year-olds and adolescents are negligible. Furthermore, those parents may differ in their understanding of the term 'wheeze'.[20,21] However, why parental interpretation of 'wheeze' would be more problematic in children with DS than in their siblings or in controls. Finally, in every case–control study, selection bias needs to be considered. As we have no data confirming the representativeness of our study population to be representative of the DS population-at-large, we have no reason to believe why we have selected a population of DS patients with recurrent wheeze from our large cohort of children with DS.

The main strengths of our study include the relatively large sample size of patients with DS and the use of a control group of siblings of children with DS, who share the genetic and environmental background with the DS cohort. The significant and relevant difference in recurrent wheeze between children with DS and their siblings indicates that recurrent wheeze in DS has a multifactorial pathophysiology that is unique to DS and is not associated with allergic airway inflammation. In our view, therefore, recurrent wheeze in DS should not be diagnosed and treated as asthma.

KEY NOTES

- Children with Down syndrome are more likely to wheeze than their siblings or controls.
- Asthma is seldom confirmed in children with Down syndrome.
- Wheeze in children with DS is likely to have a pathophysiology different from that of asthma.

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7

Quality of Life and its determinants in preschool children with Down syndrome

Michel E. Weijerman
Petra E.M. van Schie
Michiel J.M. Volman
Marceline A. van Furth
Reinoud J.B.J. Gemke

Submitted

ABSTRACT

Aim: Children with Down syndrome (DS) show delay in cognitive and motor development, and have different health problems. We compared Health-Related Quality of Life (HRQoL) in preschool children with DS with a preschool reference group, and investigated the influence of child-related factors (i.e., developmental quotient, adaptive function, health problems, problem behaviour), and maternal level of education on HRQoL in these children.

Method: In a cohort of 55 children with DS, HRQoL was measured with the TNO-AZL preschool children Quality of Life Questionnaire (TAPQoL). TAPQoL data from a reference group of preschool children (n = 318, age range 12-48 months) were used for comparison. Developmental Quotient (DQ) was assessed with the Bayley Scales of Infant Development second version (BSID-II), adaptive function was assessed with the Pediatric Evaluation of Disability Inventory (PEDI), health problems (i.e., congenital heart defect (CHD), respiratory and/or gastro-intestinal problems) were derived from the children's medical file, and behavioural problems were measured with the Child Behaviour Checklist (CBCL).

Results: The children with DS (n = 55; mean age 41.7 months SD 14.3) scored significantly lower on the TAPQoL domains lung and stomach problems, motor function and communication compared to the reference group. Mental developmental delay (lower DQ scores) had a significant negative impact on TAPQoL domains lung problems and liveliness. Children with DS with respiratory or gastro-intestinal health problems showed significant lower scores on the TAPQoL domains lung problems and communication. Problem behavior had a significant negative impact on the TAPQoL domains sleeping, appetite and social function. A low level of maternal education negatively affected the domain positive mood.

Conclusion: Parents of preschool children with DS report a lower HRQoL on particular domains of QoL compared to a reference group. HRQoL is influenced by developmental quotient, respiratory and gastro-intestinal health problems, problem behaviour and maternal education, but not by CHD and adaptive function.

INTRODUCTION

Down syndrome (DS) is the most common genetic cause of retardation with a characteristic appearance, specific physical problems and delayed cognitive and motor development. While most current studies focus on the medical aspects of DS, there is few information available on Health-Related Quality of life (HRQoL) and the determinants that may influence HRQoL in young children with DS. Medical issues like congenital heart disease (CHD) as well as delayed development, specific behavior problems, age and family context may play a role in HRQoL of these children.[1] The delay in motor development in young children with DS substantially affects functional performance most and is on average more pronounced than the delay in cognitive development.[2,3] The cognitive development of children with DS shows a deceleration between the age of 6 months and 2 years.[3] This does not imply a plateau of cognitive skills, but more an increase of cognitive skills at a slower rate, compared to the development of unimpaired children.

An important part of the cognition is influenced by the specific delay of language development of these children. Particularly the expressive language lags behind while the receptive language is usually mental age appropriate.[4-6] Furthermore motor milestones in children with DS follow a specific sequence in their performance and disturbances in the system of postural control and tone, play a key role in this regard.[7-9] The specific DS behavior phenotype emerges around 2 years of age as a result of the relative strengths in aspects of visual processing, receptive language and nonverbal social functioning and weaknesses in gross motor skills and expressive language skills.[4,7,8,10]

Within the group of children with DS there is a wide variation in functional performance and ability levels, the delayed fine motor skills play an important role in this matter.[11,12] Behavior in young preschool and school-aged children with DS consists of their atypical cognitive, language and social function, as well as the inconsistent progress in achieving or demonstrating developmental skills. Compared to normally developing controls, specific DS behavior patterns consist of stubbornness, oppositionality, inattention, difficulties in concentrating and impulsivity.[8,13] An overall still relative predictable behavior and good mood are favorable factors in children with DS.[4]

Main health problems in young children with DS consist of CHD, congenital anomalies of the gastrointestinal tract, respiratory problems and delay in motor development. Recent decades have shown a substantial increase in the life expectancy of children with DS.[14-19] This has been due mainly to the successful treatment of CHD. Furthermore preventive health care programs for these children have contributed to the improved medical outcome as well.[14-18] This better life expectancy combined with the worldwide stable prevalence of

DS provides an increasing prevalence of the total population of DS in the near future.[19-20] Children with DS born recently meet family and community attitudes as well as health care facilities, that are more positive and more informed than years ago which is likely to have positive effects on care and development.[5,21] Furthermore the family context has been found to play a role in the development of children with disabilities such as DS.[21]

Current research in children with DS mainly focuses on the medical aspects, less information is available on HRQoL, the actual achieved developmental status, functional performance and their relation with HRQoL.[15] A recent study on the HRQoL of 8-year-old children with DS revealed that their HRQoL was lower for the domains of motor functioning, autonomy, social functioning and cognitive functioning.[1] However, knowledge about the HRQoL in younger children and the factors that might influence their HRQoL is lacking.

In the present study we investigated HRQoL in children with DS aged 1 to 5 years old, compared to typically developing children, and examined associated child-related factors, such as, mental developmental delay, adaptive function, health problems, problem behavior, and maternal level of education.

METHOD

Procedure

The VU University Medical Center (VUmc) has a dedicated outpatient clinic for children with DS, which accepts children with DS referred by parents themselves, general practitioners, and pediatricians from within and outside the hospital.

Between 2005 and 2007 parents of all DS children aged 12–60 months attending this VUmc outpatient clinic were asked to participate in this study. Inclusion criteria were a cytogenetic confirmed diagnosis DS and an age of 12–60 months at the start. If the parents were not able to speak and understand Dutch was considered as exclusion criterion. The clinical examinations were performed as part of our standardized clinical routine of DS preventive health care program with permission of the parents.[15,18]

Ethical considerations

Under Dutch law, our study involving solely health related questionnaires sent to healthy adults (the parents of the children involved) and was waived submission for full consideration by the institutional review board. Informed consent was given by the parents of the children with DS who participated.

Measurements

For assessment of quality of life, the TNO-AZL Preschool children Quality of Life (TAPQoL) was used.[22,23] This is a generic instrument consisting of 43 items, covering physical, social, cognitive and emotional functioning in preschool children aged 2 to 48 months. It measures parent's perception of HRQoL, defined as health status in 12 domains weighted by the impact of the health status problems on well-being (**Figure 7.1**). Lower scores indicate a lower HRQoL. The reliability and discriminative validity of its scales for infants as well as toddlers has been reported satisfactory.[27] All parents were sent this questionnaire by mail. The results of parents of a randomly selected general population sample of 318 children aged 12–48 months were used as norm data.[27]

Cognitive abilities were measured by the mental scale of the Bayley Scales of Infant Development, second version (BSID-II).[24] The mental scale consists of 178 items. The raw scores of successfully completed items were converted to developmental age scores. Developmental Quotients (DQ) were calculated using the traditional mental age method (Mental Age/Chronological Age x 100).

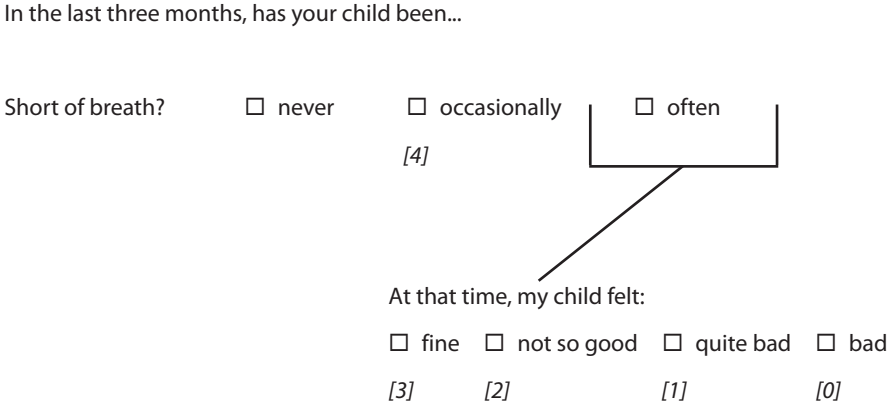

Figure 7.1 Item example TAPQOL (the scores attributed to the paired items are in italics). Reprinted with permission of Fekkes et al.[23]

Children's behavior was measured by the Child Behavior Checklist (CBCL) Parent Form either the CBCL 2-3 for children aged 2-3 years, or the CBCL 4-18 for children aged 4-18 years. The CBCL is a questionnaire containing 113 items about childhood behavior problems.[25] Based on age- and gender-dependent norm tables, the presence of externalizing problem behavior (delinquency, aggression) and internalizing problem behavior (depression, withdrawal and somatization) was assessed. The present study used the Dutch version of the CBCL, which has good psychometric properties, also in children with developmental delays.[26,27]

Adaptive function was assessed with the Dutch adaptation of the Pediatric Evaluation of Disability Inventory (PEDI). The PEDI is a standardized parent interview that examines adaptive function with regard to three domains: self-care, mobility, and social function.[2]

All children with DS were followed up at the outpatient clinic for DS patients at the VU University medical center, the attending pediatrician (MW), who examined all the children at all visits according the international guidelines of children with DS.[16,18] The medical files were used for data collection.

Maternal education was defined as higher vocational education, senior secondary vocational education and junior vocational education.

Statistical analysis

A one-sided t-test was applied to compare the TAPQoL domain scores of children with DS with the mean TAPQoL domain scores of the reference group.[22]

Association between TAPQoL domain scores and chronological age and DQ were tested with Spearman's rho rank correlation coefficient. Partial correlation analysis was applied to test the relation between TAPQoL domain scores and PEDI domain scores with chronological age as control variable. A Mann-Whitney U test was applied to test the differences between children with or without CHD, and children with or without respiratory and/or gastro-intestinal problems. A Kruskal-Wallis test was applied to test the effect of maternal education.

Analyses were carried out with SPSS version 16.0 (SPSS Inc., Chicago, IL, USA)., level of significance was set at $\alpha = .05$.

RESULTS

In our study 98 children were eligible of which 55 finally participated. Response rate was 56% over the 3 years of data collection. The main reasons for not participating were lack of time (n = 31), illnesses of the child (n = 8) and some parents had forgotten their appointment (n = 4). The children who did participate were randomly distributed among the group of 98 children. The age distribution and characteristics of the participating children are shown in **Table 7.1**. Most children (87%) were Dutch Caucasian.

In 54 children the diagnosis DS was based on trisomy 21 and one had mosaicism. The mental age is almost half as would be expected according to the chronological age (mean 21.2 versus 40.6 months respectively).

Down syndrome versus reference group

Table 7.2 shows the mean TAPQoL scores for DS and the reference group. Children with DS scored significantly lower on the domains lung problems (t = -3.34, $P < .01$), stomach problems (t = -2.17, $P < .05$), motor function (t = -8.73, $P < .001$), and communication (t = -12.99, $P < .001$) compared to the reference group, indicating a lower HRQoL on these domains. No significant differences were found for sleeping, appetite, skin problems, social functioning, problem behavior, positive mood, anxiety, and liveliness.

We did not compare BSID-II and CBCL data of the children with DS with a reference group.

Effect of chronological age on TAPQol and developmental quotient (DQ)

Table 7.3 shows a significant positive correlation between chronological age (CA) and the TAPQoL motor function score ($r_s = .50$, $P < .001$), indicating that older children with DS showed a higher score for that domain. A significant negative correlation between CA and the TAPQoL communication score was found ($r_s = -.30$, $P < .05$), indicating that older children had lower scores on communication.

Correlation analysis of TAPQoL domain scores with BISD II DQ scores revealed significant positive correlations for lung problems and liveliness($r_s = .30$, $P < .05$, $r_s = .41$, $P < .01$, respectively) indicating that children with a lower DQ (i.e., a larger mental developmental delay) had lower scores on these quality of life scales (**Table 7.3**). For communication a nearly significant effect was found ($r_s = .26$, $P = .07$), indicating a trend for a lower HRQoL for the children with less communication abilities.

Table 7.1 Characteristics of young children with DS (n = 55)

Mean chronological age in months (SD; range)	40.6 (12.8; 15–69)
Gender	
Male	30 (54.5%)
Female	25 (45.5%)
Cognition	
Mean BSID mental age (SD; range)	21.2 (6.7; 10–37)
Mean BSID developmental quotient (SD; range)	53.8 (10.1; 30–85)
Adaptive function (SD)	
Mean subscale PEDI Self care	36.2 (14.2)
Mean subscale PEDI Ambulation	44.3 (17.0)
Mean subscale PEDI Social function	35.0 (13.4)
Medical problems	
Congenital heart defect	27 (48%)
Respiratory problems	18 (32%)
Gastro-intestinal problems	11 (20%)
Problem behavior (n = 30)	
Mean CBCL T-score (SD; range)	52.8 (7.8; 33–64)
CBCL borderline/clinical range (T ≥ 60)	n = 6 (20%)
Maternal education	
Less than high school	4 (7%)
High school/general equivalency diploma	15 (27%)
More than high school	36 (65%)

Table 7.2 Mean scores and standard deviations, range and median scores on the TAPQOL scales for children with DS (n = 55) and mean scores of the reference group (n = 318)[22]

	DS			Reference
	Mean (SD)	Range	Median	Mean
Sleeping	78.5 (18.9)	25–100	75.0	78.6
Appetite	85.3 (15.4)	50–100	91.7	81.9
Lung problems	82.4 (22.8)**	16.7–100	91.7	92.7
Stomach problems	87.3 (15.8)*	50–100	95.8	91.9
Skin problems	90.6 (7.9)	66.7–100	91.7	91.0
Motor function	82.4 (12.7)***	25–100	81.3	97.8
Problem behavior	73.9 (20.3)	14.3–100	78.6	68.9
Social function	93.8 (12.5)	50–100	100	91.8
Communication	68.4 (11.6)***	18.7–87.5	68.8	89.4
Positive mood	98.5 (6.3)	66.7–100	100	97.7
Anxiety	78.2 (19.2)	33.3–100	66.8	75.8
Liveliness	96.1 (11.1)	50–100	100	96.1

* $P < .05$, ** $P < .01$, *** $P < .001$ measured by a one sided t-test.

Table 7.2 Correlations between TAPQoL domain scores and Chronological Age (CA) and Developmental Quotient (DQ)

TAPQOL scales	r_s CA	r_s DQ
Sleeping	.18	.13
Appetite	-.14	.14
Lung problems	-.06	.30*
Stomach problems	-.23	.15
Skin problems	.16	-.07
Motor function	.50**	.16
Problem behavior	-.09	.16
Social function	-.03	.22
Communication	-.30*	.26
Positive mood	-.05	.13
Anxiety	-.04	.02
Liveliness	-.20	.41**

* $P < .05$, ** $P < .01$. r_s = Spearman's rho rank correlation coefficient.

Effect of adaptive function

The mean scores on the PEDI domains self-care, mobility and social function are presented in **Table 7.1**. Partial correlation analysis (controlled for CA) did not reveal any significant relations between PEDI self-care, PEDI ambulation and PEDI social function scores and the different TAPQoL domain scores.

Effect of medical conditions

No significant differences on TAPQoL scores were found between children with or without CHD. All the CHD's had been corrected surgically when needed and at the time of the survey, haemodynamically important cardiac defects were no longer present in any of these children. The group children with DS with respiratory or gastro-intestinal problems scored significantly lower on the TAPQoL domains lung problems and communication compared to children without respiratory or gastro-intestinal problems (respectively, Z = 2.31, $P < .05$; Z = 2.31, $P < .05$; **Table 7.4**), while there was a trend in the same direction for the domain anxiety (Z = 1.83, $P = .07$). Both groups did not significantly differ in CA.

Effect of problem behavior

Significant correlations were found between TAPQoL and CBCL scores (n = 30) for the TAPQoL domains sleeping ($r_s = -.42$, $P < .05$), appetite ($r_s = -.40$, $P < .05$), social function ($r_s = -.37$, $P < .05$) and communication ($r_s = -.46$, $P < .05$). Children with higher scores on problem behavior had lower scores on these TAPQoL scales.

Table 7.4 TAPQOL scales for the DS group with and without respiratory or gastro-intestinal problems

TAPQOL scales	Respiratory and/or gastro-intestinal problems (n = 24)		No respiratory or gastro-intestinal problems (n = 31)	
	Mean	SD	Mean	SD
Sleeping	76.0	21.0	80.4	17.2
Appetite	82.3	16.4	87.6	14.4
Lung problems	74.6*	25.0	88.4	19.3
Stomach problems	84.7	17.3	89.2	14.5
Skin problems	92.0	8.7	89.5	7.2
Motor function	83.9	11.8	81.2	13.5
Problem behavior	69.6	21.8	77.2	18.7
Social function	91.0	13.9	96.3	13.8
Communication	64.6*	10.0	71.8	11.9
Positive mood	98.6	6.8	98.4	6.6
Anxiety	72.9	19.3	82.3	18.2
Liveliness	95.8	2.5	96.2	10.2

* $P < .05$ measured by a Mann-Whitney U test.

Effect of maternal education

A significant effect of maternal education on the TAPQoL domain positive mood was found ($\chi^2 = 16.1$, $P < .001$), indicating a lower HRQoL score for the low education group (M = 87.5) compared to the middle and high education group (respectively, M = 100; M = 99.1).

DISCUSSION

This study provides insight in HRQoL in 55 preschool children with DS and its relation with child-related (developmental quotient, functional status, health problems, problem behavior) and family-related (maternal education) factors. We compared HRQoL of preschool children with DS with a normative reference group, and investigated the influence of child-related factors and HRQoL of these children. In comparison with the reference group, children with DS showed a lower HRQoL on the domain of lung and stomach problems, motor function and communication. HRQoL domains were particularly affected by DS children's developmental quotient, health problems (i.e., respiratory or gastro-intestinal), problem behavior, and maternal education. CHD and children's adaptive function did not significantly affect HRQoL.

Children with DS with a larger mental developmental delay (lower DQ scores) showed a lower HRQoL for lung problems and liveliness, and a trend toward significance for

communication. Recently van Gameren et al investigated levels of development, problem behavior, and HRQoL in a population sample of Dutch eight-year-old children with DS and found comparable results, however these children were almost twice as old as in our study.[1] This study showed a substantial delay in developmental skills in comparison with a normative sample and significantly lower HRQoL scores for the scales gross motor skills, autonomy, social functioning and cognitive functioning.[1]

In our study CHD did not affect HRQoL. CHD was considered to be the most important clinical phenomenon of DS relevant to morbidity and decisive in infant mortality. However over recent decades, there has been a substantial increase in the life expectancy of children with DS. This increase in life expectancy as well as the minor role of CHD in morbidity of children with DS has mainly been due to the successful early surgical treatment of the CHD of these children and could be responsible for the favorable HRQoL results in this group of our study.[20,28] Children with DS scored significantly lower on the domain lung problems compared to the reference group, indicating a lower HRQoL on this domain.

One third of children with DS were reported to have difficulties with breathing or have other respiratory problems.[29] Both wheeze ever, wheeze during the last 12 months and recurrent wheeze were more commonly reported in DS than in their siblings or controls.[29,30] Respiratory problems are the most common reason for children with DS to be admitted to the hospital, mostly due to bronchiolitis by respiratory syncytial virus, and causes their excess mortality.[31,32] These lung related scores underscore the importance of appropriate treatment and follow up of lung problems. Asthma and allergy do not seem to play an important role in this respect.[30]

In our study we also explored problem behavior and found a significant correlation between problem behavior and the TAPQoL domains sleeping, appetite, social function and communication. Unexpectedly this was not found on the TAPQol domain problem behavior. In our study 20% of the children with DS had CBCL borderline/clinical range (T-score > 60), which is lower but comparable with the 27% found in the study of van Gameren et al. in 8 year old children with DS.[1,25] Eisenhower et al. found in children with DS at age 3, an age comparable with the children in our study, only 8% in the borderline/clinical range. The problem behavior in children with DS ranked lowest among the groups of children with development delay, like autism and even showed fewer problem behavior than typically developing children. The behavior problems in children with DS described in this study increased over time up to age 5, while typically developed children showed a decrease in total T-scores in time.[33] These results demonstrate that children with DS have more behavior problems when they get older and this may be the result of the increased

expression of their externalizing behavior, like stubbornness.[13,32] In our study the problem behavior had already impact on HRQoL at the preschool age period.

In the present study we did not find any significant effects of adaptive function (PEDI self-care, PEDI ambulation and PEDI social function scores) on HRQoL of children with DS, comparing different TAPQoL domain scores. In a study of 5 year old children with DS, Dolva et al. found a disadvantage of self care activities in those children with delayed fine motor skills.[11] Furthermore the children with DS appeared to be less affected in their functional mobility skills. In our study we did not find an effect of mobility on the TAPQoL and motor function. Studies up to now report a variation in ability levels in children with DS, our study population was relative young so the differences and their functional performance could be less pronounced at this age.[11]

Finally we studied the education level of the mothers of the children with DS. Mothers from the low level education group reported a lower HRQoL for positive mood compared to the middle and high education group.

Studies of typically developing children show the impact of aspects of families in promoting children's functioning and this may help to predict the development of children with disabilities. Hauser et al. found a significant positive correlation with mother's education level and growth in socialization domains.[21] On average, higher maternal education was associated with better developmental (HRQoL) perspectives for their DS child.[21] The family environment composite can be important in this matter and may be a significant determinant of growth in three domains: communication, daily living, and social skills.[21]

The HRQoL domain mood in our study was negatively influenced, when the mothers had a lower education level. These mothers may have more problems with coping and as such have lower well being and positive mood, which influences their child with DS.

At the same time having a child with DS may be a potential source of distress. The amount of care of the partner and the support from the environment play an important role in this matter.[34]

The present study has several limitations. Especially the small sample size of 55 children and the relative young age of the group children. The HRQoL information has been collected by proxy and may be influenced by the mood of the reporting parent.[33,34] Also we cannot exclude that the response rate may have introduced a selection bias. Although the most important results show significant differences our results should be interpreted with caution. What our study wants to emphasize is a new trend to approach HRQoL issues.

Compared to 1–2 decades ago these children had substantial limited life expectancy and a different morbidity spectrum. The current improvement of the medical issues obliges us to look into new medical issues and new opportunities for these children regarding long term developmental outcome and HRQoL.

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8

General discussion

GENERAL DISCUSSION

Down syndrome (DS) is the most common chromosomal malformation among newborns, and accounts for 8% of all registered cases of congenital anomalies. Delayed psychomotor development and an increased risk of concomitant congenital defects and organic disorders typify children with DS.

The first year mortality declined substantial and the median age of death in individuals with DS improved as well. In a survey of 17,897 individuals with Down's syndrome in the USA, the median age of death increased from 25 years in 1983 to 49 years in 1997.[1] Estimates of life expectancy suggest that about 44% of persons with DS will reach the age of 60 and 14% will reach the age of 68.[2]

Successful surgical treatment of congenital heart defect (CHD) and the improved treatment of congenital anomalies of the gastrointestinal tract, are particularly responsible for this increase in the life expectancy. Furthermore preventive health care programs have contributed to improved life expectancy and overall outcome of these children.[3,4]

As a consequence of the improved prognosis a shift in morbidity of children with DS developed, where tract problems constitute at the moment important determinants of the DS morbidity, focus should be more directed to Health-Related Quality of Life (HRQoL) aspects.[5,6]

Respiratory tract and immune respons

In our study 38% of the children with DS had ever wheeze, these findings fit with the previous findings that wheeze is a common problem in children with DS.[6] In children with DS the respiratory problems usually have a multifactorial origin and seem not related to asthma or atopy.

A low prevalence of atopic sensitization in DS is in agreement with the rare occurrence of confirmed asthma in literature and earlier work on aeroallergen sensitization both in children with DS.[6] In this respect congenital malformations such as subpleural lung cysts, pulmonary hypoplasia, and abnormalities of the tracheobronchial tree, can be responsible for the respiratory morbidity. Muscle hypotonia, upper airway obstruction and aspiration can play a role as well. Furthermore a variety of immune defects have been identified, which can lead to respiratory infections. Studies have shown abnormalities in the immunoglobulin levels in DS with IgG4 subclass deficiency. A decrease in salivary IgA and IgG have been proposed, decreases in lymphocyte markers and decreased response of lymphocytes to mitogen stimulation have been documented in patients with DS. Children with DS had

significantly lower absolute total leukocytes, lymphocytes, and monocytes, but a 1.5-times higher level of proinflammatory monocytes compared with control subjects. Abnormalities in T- and B cell function and in the innate and adaptive immune systems have been shown in children with DS as well.

In contrast to the low prevalence of atopic disease in children with DS, autoimmune disorders such as celiac disease (CD), hypothyroidism and diabetes mellitus are much more common. This may suggest a T-helper 1/2 cell imbalance or regulatory T-cell dysfunction in children with DS. Further study is needed to establish the potential immunologic defect in DS.

Despite the above suggested underlying mechanisms of wheezing in DS, wheezy children with DS are often diagnosed as having asthma and treated accordingly. Treatment with anti-asthmatic medication in these children, however, is usually unsuccessful and disappointing and should be reconsidered and emphasizes the need to consider alternative reasons for wheezing.[6] Furthermore DS was identified as an independent risk factor for severe respiratory syncytial virus (RSV) bronchiolitis.[7] RSV prophylaxis with human monoclonal antibodies in children with DS with CHD is common, but in a child without CHD, this prophylaxis has to be considered because of their risk of the more frequent and serious infections associated with RSV.

Celiac disease

Celiac Disease (CD) is one of the potential illnesses in children with DS, the prevalence of CD in children with DS (4%-15%) is worldwide significantly higher than the general population (0.3%-1.0%). In the Netherlands, we found a prevalence of CD in children with DS of 5.2%.[8] Recently we proposed beginning CD screening in the first year of life, using human leukocyte antigen(HLA)-DQ2 and HLA-DQ8 typing to identify the children with DS who are at risk for CD.[8] By performing this CD screening in the first year of life, more than half of the children with DS (60%) are negative for HLA-DQ2 or HLA-DQ8. Consequently the parents can be early reassured, that their child is not at risk for CD, the negative predictive value of the HLA-DQ typing is nearly 100%.

In the meantime observational studies suggested that breastfeeding may protect against the development of CD.[9] The meta-analysis of these studies showed that the risk of CD was markedly reduced in infants who were breastfed at the time of gluten introduction as compared with non-breastfed infants.[10]

With the current state of evidence breast milk is not yet promoted as a permanent factor of protection against CD, but breast milk can delay the onset of symptoms. Further studies like the PreventCD study can elucidate this answer.

On the basis of these data the Committee of the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) considers it prudent to introduce gluten while the infant is still breastfed and indicate a window of opportunity for a lowering risk of CD by introducing gluten (while still breastfed) into the child's diet at the age of 4-6 months.[9,10]

With this relative new information in mind the parents of the HLA-DQ2 or HLA-DQ8 positive children with DS (40%), who had not been reassured in the first place, can get a new opportunity, provided a HLA typing is performed early in life and the breastfeeding is continued for 6 months. As a consequence the moment to begin HLA-DQ screening in children with DS should be optimized and the advice should be changed into the first month of life. Consequently mothers can get the opportunity to reconsider their breastfeeding policies at this early moment. We recommend to perform the HLA-DQ typing by buccal swab, which appeared to be reliable and has the benefit of avoiding the unpleasant collection of blood.

Breastfeeding

The advice to start or continue breastfeeding in children with DS is an important and well known issue. In our study concerning DS in 2003 in the Netherlands, only 48% of the children with DS were breastfed from birth, compared with 78% in the reference population.[11] In the follow up of our study (2003-2006) in the Netherlands 48.9% of the mothers with a child with DS started breastfeeding exclusively and 13.1% of these mothers gave both breast milk and formula (total of 62%). Furthermore at least 40% of the breast milk fed children with DS got their breast milk in different ways (bottle, nasal tube). Up to now 75% of the mothers in the reference population gave their child without DS breastfeeding exclusively.

On the basis of these results there are still improvements to make concerning breastfeeding in children with DS. Up to date information must be available to both the caretakers and the parents, to help them making the right decision on breastfeeding.[11] Next to the described possible CD prevention of breast milk, breastfeeding in children with DS has specific advantages in terms of stimulating the development of the oral motor system and speech.

Genetic challenges

To understand DS, it is crucial both to understand the genomic content of chromosome 21 and how the expression of these genes are altered by the presence of a third copy of this chromosome. For instance the incidence of leukemia and testicular cancer are increased in DS, the risk of developing solid tumors is reduced. Atopic disease seems to

have a low prevalence in DS, on the other hand, autoimmune disorders like celiac disease, hypothyroidism and diabetes mellitus are much more common in DS.[12]

To develop new therapeutic goals, it is necessary to discover the identity of genes that contribute to DS phenotypes. At the moment more than 450 genes have been identified on chromosome 21.[12,13] New observations have led to the identification of the long arm of chromosome 21 as the responsible region for the DS phenotype, the DS critical region (DSCR).[13]

Genes have been identified specific related to the DSCR, for example the gene dual-specificity tyrosine-(Y)-phosphorylation-regulated kinase 1A (DYRK 1A).[12-14] Recent evidence suggests the contribution of trisomy of the gene DYRK 1A in the development of Alzheimer disease (AD), learning and memory in people with DS. In the mouse model the protection against the development of tumors required three copies of the chromosome 21 'proto-oncogene' (protein C-Ets-2), suggesting that in this context, this gene may be acting as a tumor suppressor.[12]

A number of compounds have been shown to improve learning in the trisomy mouse model. AD is a important issue in DS and appears to be the most important cause of morbidity and mortality among elderly persons with DS. Recently new presented figures show a plateau of AD in the oldest group of persons with DS not exceeding 28.6%.[2]

Therapeutic challenge for people with DS has focused on pharmacological treatment to influence their cognition. Future possibilities of regulating the function of the genes are becoming realistic in this matter.[14,15] Future prospects could be the early(childhood) preventive treatment of the neuropathological manifestations of AD, which is encoded on the β-amyloid precursor protein, located on chromosome 21, and this may influence the cognition of children with DS positive.[2] Further understanding in the DNA sequence of chromosome 21 may lead in future to new strategies.[14]

Prevalence

Next to the change in morbidity and life expectancy in DS, time have changed the way in which the prevalence of DS has been influenced and still is. Prevalence of DS is dependent on a lot of variables, but is mainly influenced by the background of the pregnant woman (cultural, socioeconomic, racial, religious, age of the mother and society's law).

Worldwide there was an increase in prevalence of DS starting around the end of the last century and stabilized up to now. The trend of the prevalence of DS in the Netherlands is shown in the figure, estimated on the base of extrapolation of two coupled files, the National

Dutch Neonatal (LNR) and Obstetric (LVR) Registries (Figure 8.1).[15] The estimated prevalence's are lower as compared with the use of more extended file comparison, but are reliable for the trend.[11]

The prevalence of DS is particularly dependent on the use of prenatal tests and on the decision of mothers and their partners to terminate or to continue their pregnancy. Furthermore the detection rate of DS pregnancies is important, for instance in the Netherlands this is around 76%, which is low as compared to other countries.[16] The currently used first trimester test is made by the maternal serum concentrations of pregnancy-associated plasma protein A(PAPP-A) and free beta human chorionic gonadotropin (fβ-hCG) and an ultrasound measurement of the foetal crown-rump length (CRL) and of the foetal nuchal translucency (NT). These results are combined with the maternal age to give a risk estimate of getting a child with DS. The performance of these tests could rise to a maximum of almost 90% in the future by drawing two samples during the first trimester and adding potential biochemical screening markers.[16]

Up to now the uptake of these prenatal tests is low in the Netherlands. For example in 2009 the uptake of this match test in the Netherlands was no more than 25.7% (2004-2006: 23%, 2008: 23.7%). In other European countries the uptake is reported to be around 80%.[17,18] The current prenatal screening policies vary much worldwide currently and may lead to different outcomes of prenatal diagnosis and as a consequence to equivocal decisions on terminations of pregnancies in a early stage. As a consequence prevalence of DS in both live and still born will change. Early prenatal detection of DS will detect more DS pregnancies, which would have ended otherwise in a natural miscarriage, according to literature up to 25-30% and live birth prevalence may fall as a consequence of prenatal testing and termination of pregnancies.[19] Furthermore prevalences of CHD and other detectable

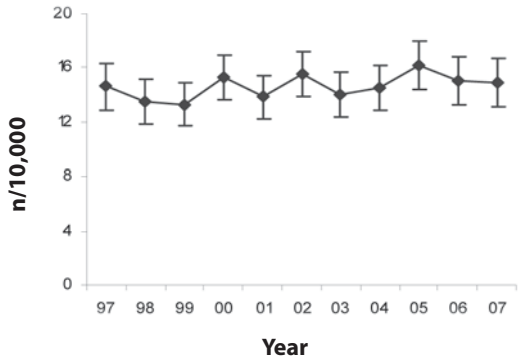

Figure 8.1 Trend of the prevalence of Down syndrome (DS) in the Netherlands (number of children with DS/10,000 live born).[15]

congenital anomalies follow these developments in a similar way. In 2003 in addition 33% of the mothers of newborns with DS were ≥ 36 years and must have been aware of their choice, since tests are being offered active in the Netherlands to mothers ≥ 36 years.

In the Netherlands as well as in other European countries, the percentage of mothers of 35 years of age or more has risen significantly. The proportion of mothers aged 36 and above has increased from 8% to 25% over the last 30 years in Europe and in the Netherlands from 10.8% to 22.4% up to now.[11,19] The effect of maternal age and the awareness of mothers not to test, despite the availability of advanced prenatal screening tests, is important. The balance of this choice and of the terminations of DS pregnancies results in a net effect of a stable prevalence of live born children with DS up to now.

The forthcoming availability of new DS diagnostic tests, could influence the birth rate of DS. Especially non-invasive detection of fetal trisomy 21 by sequencing maternal plasma DNA will play an important role in the future developments of prenatal screening and diagnosis.[20] These new tests could be offered in the first trimester before women begin to show and endure physical signs of their pregnancies. Consequently, women will be able to receive a DS diagnosis and make a decision about the continuation of their pregnancies in private and before the pregnancy is in progress. If desired, a woman could decide to terminate without anyone ever knowing that she was pregnant and more important before she has been physical and maybe too emotional involved.

The new tests are non-invasive, carrying no risk to the fetus, unlike chorionic villus sampling (CVS) and amniocentesis. Furthermore these new tests are projected to cost less than amniocenteses or CVS. As a result, health insurances might readily shift to covering the new tests.[21] On the other hand up to now a relative high percentage of pregnant women decide not to test. A substantial percentage of these women is ≥ 36 years and despite their age risk of getting a child with DS, they make the decision.

Health-related quality of life

In the meantime recent data show a stable DS prevalence, a better insight in DS morbidity and better treatment results in children with DS. These children live longer and the medical care improves so determinants of this longer life, the health-related quality of life (HRQoL) needs to be explored.

In our study preschool children with DS scored significantly lower on lung and stomach problems, motor function and communication as compared to the reference group. Older children with DS showed a better HRQoL, but had lower scores on communication and liveliness. HRQoL scores in children with DS with or without a CHD did not differ.

Our goals for treatment should be altered and attention should be given to the underlying causes which influences HRQoL in children with DS, like respiratory morbidity, motor function and communication.

FUTURE PERSPECTIVES

Nowadays the outcome of medical aspects and mortality is improved and DS is more accepted in the Western World. Children with DS born recently meet family and community as well as health care attitudes, that are more positive and DS educated than years ago. The DS phenotype is well understood so we are better prepared to support the child with DS and their families. Current research supports the idea that brothers and sisters are more positively impacted by a sibling with DS rather than adversely affected.[22]

Parents who have a child with DS have already found much richness in life with an extra chromosome, so they often reflect positively[23] (also personal experience). However, more work has to be done on the understanding of families and community processes that optimize function and independent living.[14] At the moment a stable DS prevalence is seen, what parents will decide in future will be the question. In the parents process of making a decision, whether to continue or stop their DS pregnancy a pediatrician with sufficient knowledge of the current well-being of children with DS can play an important even central role for these parents.[24]

The prevalence of DS will always be the net effect of the balance of the technical possibilities on the one hand and the personal feelings of the future parents on the other hand and is not easy to predict on the base of evidence only. Meanwhile our responsibility must be to optimize the medical health care programs for children with DS and to improve the treatment of known problems and to focus on new QoL issues.

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Summary

This thesis describes the current state of children with Down syndrome (DS) in relation to the prevalence, morbidity, mortality and quality of life. DS is one of the most common chromosomal abnormalities and is characterized by several dysmorphic features and delayed psychomotor development. Children with DS also have an increased risk of concomitant congenital defects and organic disorders such as congenital heart defect (CHD) and gastrointestinal defects, celiac disease (CD) and hypothyroidism.

Because of medical improvements in overall DS related medical care, the survival of individuals with DS has increased considerably. The median age at death of individuals with DS has risen significantly, in the US for instance there was a rise from 25 years of age in 1983 to 49 in 1997. Estimates of life expectancy suggest, that about 44 % of persons with DS will reach the age of 60 and 14 % will reach the age of 68 in the near future. This life expectancy requires giving the necessary care to the individual with DS over their total longer lifespan, this should be taken into account.

Chapter 2 describes the morbidity and strategies on the base of "best evidence", based on the most relevant literature currently available for optimal care of the child with DS. CHD and respiratory infections are the most frequently reported medical disorders on death certificates for individuals with DS.

Chapter 3 describes the prevalence, neonatal characteristics, and first-year mortality of children with DS. To a large extent, the prevalence of DS depends on socio-cultural variables. In countries where abortion is illegal such as Ireland and the United Arab Emirates, its prevalence is higher. Conversely, in France DS prevalence is low, and this is probably due to a high percentage of DS pregnancy terminations. In our study we estimated the DS prevalence in The Netherlands in 2003 at 16 per 10,000 live births, an almost 1½ time increase compared with Eurocat registrations in the northern Netherlands between 1981 and 1990, which show DS prevalences of respectively 10.6 per and 12.8 per 10,000 live births. Increasing maternal age and improved survival rates for infants with Down syndrome have outweighed the effects of prenatal diagnosis followed by the termination of pregnancy and a declining general birth rate. Recent decades have seen a substantial increase in the life expectancy of children with DS. In The Netherlands, the infant mortality rate in children with DS dropped from 7.07% in 1992 to 4% in 2003, this is in contrast with the 0.48% infant mortality of the reference population in The Netherlands in 2003. The fall in DS mortality was mainly related to the successful early surgical treatment of CHD and to the improved treatment of congenital anomalies of the gastrointestinal tract. The life expectancy of children with DS is primarily dependent on the risk of mortality in the first year of life. Furthermore our study showed remarkable observations, children with DS were less often breast-fed and 86% of the children with DS were hospitalized after birth.

Chapter 4 describes the prevalence of CD. We found a prevalence of CD in children with DS of 5.2% (10 times higher than the general Dutch population). In our study blood samples were taken from all 155 studied children with DS, and random we collected buccal swabs from 9 of them. Human leukocyte antigen (HLA)-DQ typing was performed, and immunoglobulin A anti-endomysium-(EMA) and anti-tissue transglutaminase antibodies (TGA) were measured. HLA-typing obtained on buccal swabs from the children with DS has the benefit of avoiding the unpleasant collection of blood. Sixty-three children (40.6%) had test results that were positive for HLA-DQ2 or HLA-DQ8. Results of HLA DQ-typing of DNA isolated from blood and buccal swabs were identical. Eight of the children in whom test results were positive for HLA-DQ2/8 also had positive test results for EMA and TGA. CD was confirmed in 7 of these children with an intestinal biopsy, and in 1 child, CD was suggested with improvement on a gluten-free diet. We recommend on the base of our results and literature HLA-DQ2/8 typing from buccal swabs in the first year of life and initiating serologic screening of children with DS in whom test results are positive for HLA-DQ2 or DQ8 at age 3 years. This would allow the further selection of a group needing to be screened and a group that can be excluded from further screening because the negative predictive value of the HLA-DQ typing is almost 100%. Early knowledge of negative HLA-DQ2/8 status can reassure those parents that their children do not have a CD risk. A positive HLA-DQ2/8 status may give the parents of the children with DS the opportunity to use preventive options (**Chapter 8**).

Chapter 5 describes the assessment of the prevalence of CHD and persistent pulmonary hypertension of the neonate (PPHN) in children with DS and the impact of CHD on neonatal factors. It was a prospective study of a birth cohort of children with DS born between 2003 and 2006 registered by the Dutch Paediatric Surveillance Unit. A CHD occurred in 43% of 482 children with trisomy 21. Atrioventricular septal defect was found in 54%, ventricular septal defect in 33.3% and patent ductus arteriosus in 5.8%. The incidence of PPHN in DS was 5.2%, which is significantly higher than the general population. The reported mortality in newborns with DS was overall 3.3% and was still significant higher in children with a CHD versus no CHD (5.8% versus 1.5%). The presence of a CHD in children with DS had no influence on their birth weight, mean gestational age and Apgar score.

Chapter 6 decribes the frequently occurring respiratory problems in children with DS. Recurrent wheezing has been reported in more than one-third of children with DS. The aim of this study was to compare the prevalence of current wheeze in children with DS, their siblings, and nonrelated population controls. This was a case-control study in which the International Study of Asthma and Allergy in Childhood questionnaire for respiratory symptoms was completed by parents of 130 children with DS, for 167 of their siblings, and

by the parents of 119 age- and sex-matched control children from the general population. Both wheeze ever and wheeze during the last 12 months were more commonly reported in DS than in their siblings or controls. The relative risk of current wheeze in DS was 2.8 compared with siblings, and 2.75 compared with controls. A doctor's diagnosis of asthma was found in 3.1% in children with DS, in 4.2% in siblings and in 6.7% in controls. During 4-years follow-up, the diagnosis of asthma could not be confirmed in the 24 DS children with current wheeze, and atopy was found in none of them. In children with DS and wheeze a number of DS specific pathophysiological factors should be considered, like anatomical and immunological problems. Wheeze is common in children with DS, we found it likely to be related to the factors specific for DS and probably unrelated to asthma and atopy.

Chapter 7 describes Health-Related Quality of Life (HRQoL) in preschool children with DS, compared to a reference group and identifies determinants for HRQoL. HRQoL was measured with the TNO-AZL preschool children Quality of Life Questionnaire (TAPQoL). Mental development was assessed by means of the Bayley Scales of Infant Development second version (BSIDII). Behavioural problems were measured with the Child Behavior Checklist (CBCL), functional status was assessed with the Dutch adaptation of the Pediatric Evaluation of Disability Inventory (PEDI). Health problems were studied using the medical file. Maternal education was defined as higher-, senior secondary- or junior vocational education. Fifty-five children with DS (mean age 40.6 months SD 12.8) and their parents participated in this study. In our study of preschool children with DS the HRQoL is influenced by developmental quotient, respiratory and gastro-intestinal health problems, problem behaviour, and maternal education, but not by CHD and adaptive function. Our goals for treatment should be altered and attention should be given to the underlying causes which influence HRQoL in children with DS.

Conclusion (Chapter 8)

Nowadays the outcome of medical aspects and mortality is improved and DS is more accepted in the Western World. Children with DS born recently meet family and community as well as health care attitudes, that are more positive and DS educated than years ago. The DS phenotype is well understood so we are better prepared to support the child with DS and their families. However, more work has to be done on the understanding of families and community processes that optimize function and independent living. In the parents' decision-making process, whether to continue or stop their DS pregnancy a pediatrician with sufficient knowledge of the current well-being of children with DS can play an important even central role for these parents. The prevalence of DS will always be the net effect of the balance of the technical possibilities on the one hand and the personal feelings of the future parents on the other hand and is not easy to predict on the base of evidence only.

Gevolgen van het syndroom van Down voor patiënt en gezin

Samenvatting (Summary in Dutch)

Dit proefschrift beschrijft de huidige stand van zaken met betrekking tot kinderen met het syndroom van Down (DS) in relatie tot de prevalentie, morbiditeit, mortaliteit en kwaliteit van leven (KvL). DS is één van de meest voorkomende chromosomale afwijkingen en wordt gekarakteriseerd door verschillende dysmorfe kenmerken en een vertraagde psychomotore ontwikkeling. Kinderen met DS hebben ook een verhoogd risico op begeleidende aangeboren en orgaanafwijkingen, zoals aangeboren hart- en maag-darmafwijkingen, coeliakie en hypothyroidie.

Dankzij de verbeteringen in de totale DS-gerelateerde medische zorg, is de DS-overleving sterk verbeterd. De mediane leeftijd bij overlijden bij het DS is significant gestegen. In de Verenigde Staten bijvoorbeeld betrof het een stijging van de mediane leeftijd bij overlijden van 25 jaar in 1983 tot 49 jaar in 1997. Voorspellingen met betrekking tot de levensverwachting suggereren, dat al in de nabije toekomst rond de 44% van de mensen met DS de leeftijd van 60 zullen bereiken en 14% zelfs de leeftijd van 68.

Deze levensverwachting maakt het noodzakelijk dat ook gedurende deze totaal langere levensduur de noodzakelijke zorg voor mensen met het DS nodig is en daar zal rekening mee moeten worden gehouden.

Hoofdstuk 2 beschrijft de morbiditeit en strategieën op basis van het best beschikbare bewijs ("best evidence"), gebaseerd op de meest relevante en huidige beschikbare literatuur passend bij optimale zorg aan het kind met DS. Aangeboren hartafwijkingen en respiratoire infecties zijn de meest frequent gerapporteerde medische aandoeningen op overlijdensaktes van personen met DS.

Hoofdstuk 3 beschrijft de prevalentie, neonatale kenmerken en mortaliteit in het eerste levensjaar van kinderen met het DS. De prevalentie van het DS wordt voor een groot deel bepaald door socio-culturele variabelen. In landen waar abortus illegaal is, zoals bijvoorbeeld Ierland en de Verengde Arabische Emiraten, is de prevalentie hoger. Daarentegen is in Frankrijk de DS-prevalentie laag en dit is waarschijnlijk het gevolg van het hoge percentage DS-zwangerschapsonderbrekingen aldaar.

In onze studie berekenden wij een DS-prevalentie in Nederland in 2003 van 16 per 10.000 levend geborenen, bijna anderhalf maal zoveel vergeleken met de Eurocatregistraties in Noord-Nederland tussen 1981 en 1990, met DS-prevalenties van respectievelijk 10,6 en 12,8 per 10.000 levend geborenen.

De hogere leeftijd van de moeders en de verbeterde overleving van zuigelingen met het DS hebben de effecten van de prenatale diagnostiek gevolgd door zwangerschapsbeëindiging en de daling van het geboortecijfer overtroffen. In de afgelopen decennia was er sprake van een behoorlijke toename van de levensverwachting van kinderen met het DS. In

Nederland daalde de mortaliteit bij kinderen met DS in het eerste levensjaar van 7% in 1992 tot 4% in 2003. Dit is nog steeds in tegenstelling met de 0,48% mortaliteit in het eerste levensjaar bij kinderen in de referentiepopulatie in Nederland in 2003. De daling van de DS-mortaliteit wordt vooral verklaard door de succesvolle vroege chirurgische behandeling van aangeboren hartafwijkingen en de verbeterde behandeling van aangeboren afwijkingen van het maag-darmstelsel. De levensverwachting van kinderen met het DS is vooral afhankelijk van het risico op overlijden in het eerste levensjaar. Onze studie toonde tevens enkele opmerkelijke bevindingen, zoals de observatie dat kinderen met DS minder vaak borstgevoed werden en dat 86% van de kinderen met DS vlak na de geboorte werd opgenomen in een ziekenhuis.

Hoofdstuk 4 beschrijft de prevalentie van coeliakie. We vonden een prevalentie van coeliakie bij kinderen met het DS van 5,2%. Dat is zo'n 10 keer vaker dan bij de algemene Nederlandse bevolking. Bij alle 155 kinderen met DS die aan onze studie deelnamen werden bloedmonsters afgenomen en random bij 9 van hen ook wanguitstrijkjes. Een humaan leukocyten antigeen (HLA)-DQ-typering werd verricht en de immunoglobulin A anti-endomysium-(EMA) en anti-tissue transglutaminase antilichamen (TGA) werden bepaald. HLA-typering verkregen bij de kinderen met DS door middel van een wanguitstrijkje heeft het grote voordeel voor het kind dat er geen vervelende bloedafname hoeft te worden verricht.

Drieënzestig kinderen (40,6%) hadden positieve testresultaten voor HLA-DQ2 en/of HLA-DQ8. Het resultaat van de HLA-DQ-typering van het DNA geïsoleerd uit het bloed en door middel van het wanguitstrijkje was identiek. Acht van de kinderen die een positief resultaat hadden voor HLA-DQ2/8 waren ook positief voor EMA en TGA. Coeliakie werd in zeven van hen bevestigd door middel van een darmbioptie en in één van hen werd coeliakie overwogen op basis van een verbetering na gebruik van een glutenvrij dieet.

Op basis van onze resultaten en de literatuurbevindingen raden wij aan om een HLA-DQ2/8-typering te verrichten door middel van een wanguitstrijkje in het eerste levensjaar en over te gaan tot serologische screening bij kinderen met het DS, die HLA-DQ2 of -DQ8 positief zijn, op de leeftijd van 3 jaar. Hierdoor ontstaat een selectie van kinderen met het DS die gescreend moeten worden en een groep kinderen die geen verdere coeliakiescreening meer nodig hebben, omdat de negatief voorspellende waarde van de HLA-DQ-typering bijna 100% is.

Het vroeg in het leven bekend zijn van de negatieve HLA-DQ2/8-status stelt de ouders gerust dat hun kind met het DS geen risico op coeliakie heeft. Een positieve HLA-DQ2/8-status stelt de ouders van kinderen met het DS in staat gebruik te maken van preventieve mogelijkheden (**Hoofdstuk 8**).

Hoofdstuk 5 beschrijft de prevalentie van aangeboren hartafwijkingen en persisterende pulmonale hypertensie van de neonaat (PPHN) bij kinderen met het DS en de impact van hartafwijkingen op de neonatale factoren. Het betrof een prospectieve studie van een geboortecohort van kinderen met het DS, geboren tussen 2003 en 2006, geregistreerd door het Nederlands SignaleringsCentrum Kindergeneeskunde (NSCK). Een aangeboren hartafwijking werd gevonden bij 43% van de 482 kinderen met een trisomie 21. Een atrioventriculair septumdefect werd gevonden bij 54%, een ventrikel septumdefect bij 33,3% en een persisterende open ductus Botalli bij 5,8%. De incidentie van PPHN bij het DS was 5,2%, hetgeen significant hoger was dan in de algemene populatie.

De gerapporteerde mortaliteit bij pasgeborenen met het DS was in totaal 3,3% en was nog steeds significant hoger bij kinderen met DS met een aangeboren hartafwijking in vergelijking tot de kinderen zonder hartafwijking (5,8% versus 1,5%). De aanwezigheid van een aangeboren hartafwijking bij kinderen met het DS had geen invloed op hun geboortegewicht, gemiddelde zwangerschapsduur en Apgarscore.

Hoofdstuk 6 beschrijft de vaak optredende longproblemen bij kinderen met het DS. Terugkerend piepen ("recurrent wheeze") wordt in meer dan een derde van de kinderen met het DS gerapporteerd. Het doel van onze studie was om de prevalentie van actueel piepen ("current wheeze") bij kinderen met het DS te vergelijken met hun broertjes en zusjes en met een niet-gerelateerde controlepopulatie. Het betrof een case-controlstudie, waarbij de "International Study of Asthma and Allergy in Childhood" vragenlijst bedoeld voor respiratoire klachten werd ingevuld door de ouders van 130 kinderen met het DS, voor 167 van hun broertjes en zusjes en door de ouders van 119 voor leeftijd en geslacht vergelijkbare controlekinderen uit de algemene populatie. Zowel het antwoord op ooit piepen ("wheeze ever") als op piepen ("wheeze") gedurende de laatste 12 maanden werd vaker gerapporteerd bij kinderen met het DS dan bij hun broertjes en zusjes, alsook bij de controlegroep. Het relatieve risico op het krijgen van "current wheeze" was 2,80 vergeleken met de broertjes en zusjes en 2,75 vergeleken met de controlegroep. Een door een arts bevestigde diagnose astma werd bij 3,1% van de kinderen met DS gevonden, vergeleken met 4,2% bij de broertjes en zusjes en 6,7% bij de controlegroep. Gedurende de 4 jaar lange vervolgperiode werd bij géén van 24 kinderen met het DS met "current wheeze" de diagnose astma bevestigd, bovendien werd er ook bij geen van hen atopie aangetoond.

Bij kinderen met het DS en klachten van piepen, valt een aantal DS specifieke pathofysiologische factoren te overwegen, zoals anatomische en immunologische factoren. Piepen komt vaak voor bij kinderen met het DS. Wij achten het waarschijnlijk dat de oorzaak hiervan vooral samenhangt met DS-specifieke factoren en waarschijnlijk niet past bij astma en/of atopie.

Hoofdstuk 7 beschrijft zowel de gezondheidsgerelateerde kwaliteit van leven (KvL) van peuters (1-5 jaar) met DS, vergeleken met een referentiegroep, alsook de determinanten die bepalend zijn voor hun KvL. KvL werd gemeten met de "TNO-AZL preschool children Quality of Life Questionnaire" (TAPQoL). De mentale ontwikkeling werd bepaald door middel van de "Bayley Scales of Infant Development second version" (BSIDII). Gedragsproblemen werden gemeten met de "Child Behavior Checklist" (CBCL), de functionele status werd gemeten met de aangepaste Nederlandse versie van de "Pediatric Evaluation of Disability Inventory" (PEDI). Gezondheidsproblemen werden bestudeerd aan de hand van de medische statussen. Het opleidingsniveau van de moeder werd gedefinieerd als hoger, middelbaar en lager beroepsonderwijs. Vijfenvijftig kinderen met DS (gemiddelde leeftijd 40,6 maanden SD 12,8) en hun ouders namen deel aan deze studie. In onze studie werd de gezondheidsgerelateerde KvL beïnvloed door het ontwikkelingsquotiënt (development quotient, DQ), long- en maagdarmgezondheidsproblemen, probleemgedrag en het opleidingsniveau van de moeders. Aangeboren hartafwijkingen en adaptieve functies daarentegen hadden geen invloed op de KvL.

Onze toekomstige behandeldoelen bij kinderen met het DS zouden moeten worden gewijzigd en er zou aandacht moeten worden besteed aan de problemen die gezondheidsgerelateerde KvL bij kinderen met het DS beïnvloeden.

Conclusie (Hoofdstuk 8)

Op dit moment is het resultaat van medische zorg en de mortaliteit bij kinderen met het DS verbeterd en het DS wordt meer geaccepteerd in onze westerse wereld. Kinderen die onlangs geboren zijn met het DS, ondervinden een andere, positievere houding bij familie en omgeving, maar ook bij de werkers in de gezondheidszorg. Tevens is het op DS gerichte kennisniveau beter dan jaren geleden.

Het DS-fenotype is een inmiddels bekend en goed te voorspellen beeld, waardoor we beter in staat zijn om de juiste hulp te bieden aan kinderen met het DS en hun familie. We zullen eraan moeten werken om tot een beter begrip voor de families te komen en om het beleid voor mensen met het DS te optimaliseren om te kunnen functioneren en onafhankelijk te leven.

In het besluitvormingsproces van ouders of zij hun DS-zwangerschap voortzetten of beëindigen kan een kinderarts met voldoende kennis over het actuele beeld van het welzijn van kinderen met het DS een belangrijke, zelfs centrale, rol spelen voor deze ouders.

De prevalentie van het DS zal altijd het netto-effect zijn van de balans tussen de technische mogelijkheden aan de ene kant en het persoonlijk gevoel van toekomstige ouders aan de andere kant en is moeilijk te voorspellen aan de hand van het best beschikbare bewijs ("evidence") alleen.

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De Downpoli in het VUmc is ontstaan op het moment dat ik Will Busweiler eind 1999 had

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About the author

CURRICULUM VITAE

Michel Weijerman was born on February 24th, 1955 in Amsterdam, the Netherlands. He graduated secondary school at the 'St. Nicolaas lyceum' (HBS-B) in Amsterdam and started his medical training at the Vrije Universiteit in Amsterdam in 1972. After obtaining his medical degree in 1981, he started his training in pediatrics at the Onze Lieve Vrouwe Gasthuis (department head: dr. L.H.B.M. van Benthem †) in Amsterdam. In 1983 he continued his pediatric training at the Emma Children's Hospital, Amsterdam (department head: prof.dr. P.A. Voûte †) and did his neonatological training at the Academical Medical Center (AMC), Amsterdam (department head: prof.dr. J.G. Koppe). He completed his training in pediatrics in February 1986, and then started working as a pediatric consultant in the Zaans Medical Center in Zaandam up to 1995. He continued his work as a pediatric consultant in Amstelveen at the Amstelland hospital up to 1999. At that time his career faced a new challenge, when he was asked to join the academical setting at the department of pediatrics of the VU University Medical Center (department head: prof.dr. J.J. Roord), where he started as chief of the outpatient pediatric clinic and as associate professor of pediatrics. In this setting he was able to broaden his interest field and he got the opportunity to start a pediatric Down syndrome (DS) outpatient clinic in the VU University Medical Center. He initiated research on the well-being of children with DS, which became even more feasible when the national DS registration started in 2003 (Dutch Pediatric Surveillance Unit, NSCK), which was accomplished under his supervision. In October 2009 a new challenge presented at the Rijnland hospital in Leiderdorp, where he continued his work as chairman of the pediatrics section and as pediatric consultant, with the possibility to work with a specialized Down team for children.

Michel is married to Guusje Moll van Charante and lives in Leiden and is the proud father of daughters June (1993), Puck (1995), Pomme (1997), Kayte (2006) and son Tjidde (2009).

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List of co-author affiliations

L.R. de Baaij
Department of Pathology, VU University Medical Center, Amsterdam, The Netherlands

B.M.E. von Blomberg-van der Flier, PhD
Department of Pathology, VU University Medical Center, Amsterdam, The Netherlands

P.L.P. Brand, MD, PhD
Princess Amalia Children's Clinic, Isala klinieken, Zwolle, The Netherlands

C.J.M. Broers, MD
Department of Pediatrics, VU University Medical Center, Amsterdam, The Netherlands

J.B.A. Crusius, PhD
Department of Pathology, VU University Medical Center, Amsterdam, The Netherlands

A.M. van Furth, MD, PhD
Department of Pediatrics, VU University Medical Center, Amsterdam, The Netherlands

R.J.B.J. Gemke, MD, PhD
Department of Pediatrics, VU University Medical Center, Amsterdam, The Netherlands

M.D. Mooren
Department of Pediatrics, VU University Medical Center, Amsterdam, The Netherlands

L. Rammeloo, MD
Department of Pediatrics, Subdivision of Pediatric Cardiology, VU University Medical Center, Amsterdam, The Netherlands

P.E.M. van Schie, PhD
Department of Physiotherapy, VU University Medical Center, Amsterdam,The Netherlands

M.W.J. Schreurs, PhD
Department of Pathology, VU University Medical Center, Amsterdam, The Netherlands

M.J.M. Volman, PhD
Research Centre for Cognitive and Motor Abilities, Utrecht University, Utrecht, The Netherlands

A. Vonk Noordegraaf
Department of Pediatrics, VU University Medical Center, Amsterdam, The Netherlands

M.M. van Weissenbruch, MD, PhD
Department of Pediatrics, Subdivision of Neonatology, VU University Medical Center, Amsterdam, The Netherlands

J.P. de Winter, MD, PhD
Department of Pediatrics, Spaarne Hospital, Hoofddorp, The Netherlands

J. Wouters
Department of Pediatrics, VU University Medical Center, Amsterdam, The Netherlands

J.P. van Wouwe, MD, PhD
TNO, Quality of Life, Leiden, The Netherlands