Chapter 6

Significant impact of recurrent respiratory tract infections in children with Down syndrome

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Abstract

Objective: Parents and health professionals believe that recurrent respiratory tract infections (RRTI) have a large impact on children with Down syndrome (DS). We studied the relation between parent reported RRTI on development, behavior, and health related quality of life (HRQoL) in 8-year-old children with DS.

Method: During a 3-year period, 325 children with DS were recruited for inclusion in this observational study. Parents were asked to fill in the Child Behavior CheckList and TNO-AZL Children's Quality of Life Parent Form. A psychological assistant administrated the McCarthy Scales of Children's Abilities. The children were divided into a group with presence of RRTI ($RRTI^+$) and a group without RRTI ($RRTI^-$), on the basis of parental report. Linear regression analyses were performed to assess the effect of RRTI, while correcting for the influence of confounders.

Results: Compared to $RRTI^-$ children (n=176), $RRTI^+$ children (n=149, 46%) showed decreased mental and motor development (mean developmental age 3.67 vs. 4.08 years), more behavioral problems and lower scores on most HRQoL scales ($p<0.05$). Moreover, school enrollment is less favorable in $RRTI^+$ children.

Conclusion: In 8-year-olds with DS, the children with parent reported RRTI show more delayed development, more behavioral problems, and lower HRQoL compared to the children without RRTI. Although this association does not prove a causal relationship, further studies should focus on this, because RRTI are potentially preventable.

Key message

- Children with Down syndrome are known to be at increased risk of recurrent respiratory tract infections.
- In 8-year-old children with Down syndrome, parental report of recurrent respiratory infections was associated with more delayed development, increased risk of behavioral problems and lower health-related quality of life.

Introduction

Down Syndrome (DS) is one of the most common genetic causes of intellectual disability in children. In the Netherlands, the prevalence is approximately 1 in 714 live born infants.[1,2] Facial dysmorphic features, hypotonia, and congenital heart defects (CHD) are variably present in newborns with DS. Also, DS is associated with celiac disease, thyroid disease, diabetes mellitus, and hematological malignancies.

Respiratory complications are common in children with DS. The risk of anatomic abnormalities, respiratory syncytial virus infection and viral induced wheezing is increased.[3-5] Recurrent lung and/or airway infections (recurrent respiratory tract infections; RRTI) are frequently encountered in children with DS.[5] Parents often report delayed development due to these RRTI. Up to now, this has been studied only once in toddlers: motor development was delayed 0.88 months in 2-year-old children with DS suffering from recurrent lung or airway disease, however mental development was not affected.[6]

In this study, we measure the association between RRTI, based on parental report, and development, behavior, and health related quality of life (HRQoL) in 8-year-old children with DS.

Methods

Study population

All members of the Dutch DS Foundation having a child with DS turning 8 years of age between January 2000 and January 2003 were invited to participate in this study. If parents agreed to participation, they returned their written informed consent to the researchers. Parents were then contacted to plan a home visit for psychological testing, and a set of questionnaires was sent to them.

Social and medical background

A questionnaire asked for information on social background and demographic variables concerning family situation, breastfeeding (>1 month after birth), and attendance to childcare and school. The level of parental education was used as indicator for socioeconomic status. The medical history of the child was evaluated by routine questions. We asked parents “Does your child suffer from chronic airway infections (i.e., often severe common cold or bronchitis)” and “Was your child diagnosed with asthma?” to evaluate respiratory complaints. Response categories for both questions were “yes” or “no”. Based on the response to the first question, children were divided into children with RRTI ($RRTI^+$) and children without RRTI ($RRTI^-$). In the same way, the presence of frequently encountered diseases in DS, such as CHD, gastrointestinal disease, thyroid dysfunction, diabetes mellitus, impaired hearing and/or eye disease was noted.

Developmental skills

The Dutch version of the McCarthy Scales of Children's Abilities (MSCA) for children aged 2.5 to 8.5 years was used to measure general developmental skills.[7] An experienced and trained psychological assistant performed this test as soon as possible after the eighth birthday of the child. The MSCA contains 18 subtests, which are grouped into verbal, perceptual, quantitative, memory, and motor skills. In addition, a general cognitive scale and the developmental age of the child can be determined as well with the MSCA.

Emotional and behavioral functioning

The presence of emotional and behavioral problems was determined by the Dutch version of the Child Behavior Checklist (CBCL).[8] This test was created for children aged 4 to 12 years and contains a total of 118 items on the following 9 scales: withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention problems, delinquent behavior, aggressive behavior and sexual problems. The scales of withdrawn, somatic complaints and anxious/depressed are combined for assessing internalizing problems as a separate score. The score for externalizing problems is comprised by the scales of delinquent and aggressive behavior.

We chose the CBCL because we wanted to compare the presence of behavioral problems in children with DS to healthy Dutch children, for which reference data is available. Besides, the manual and data on validity of the Developmental Behavior Checklist – specifically designed for children with developmental problems – were not yet available in the Netherlands at the time of writing of the study-proposal.

Health related quality of life

The TNO-AZL Children's Quality of Life Parent Form (TACQOL-PF) questionnaire for children aged 5 to 15 years was used to determine the HRQoL.[9] The 57 items are grouped in physical complaints, gross motor skills, autonomy, cognitive functioning, social functioning, positive emotions, and negative emotions. With this questionnaire parents indicated health status problems in their child and also reported negative emotions expressed by the child to these problems.

Statistical analysis

To determine differences between the group of children with parent-reported RRTI and the group without RRTI ($RRTI^+$ and $RRTI^-$, respectively), we performed chi-square tests for all variables mentioned in "Social and medical background". Age was compared between both groups by an independent *t*-test. Linear regression analyses were performed to assess the association between RRTI and each of the three outcome variables separately: MSCA, CBCL, and TACQOL-PF. Gender, level of parental education, presence of siblings, childcare attendance, being breastfed and morbidity (CHD, diagnosis of asthma, gastrointestinal

disease, eye disease, impaired hearing, and thyroid dysfunction) were used as confounders. The effect sizes were computed as Cohen's f^2, which is the effect size index for multiple regression (see for formula Cohen, 1988, p. 410).[10] If f^2 equals 0.01 for a variable, it means that this variable uniquely accounts for 1% of the variance in the outcome variable (expressed as a proportion of the unexplained variance). When comparing the effect sizes for different outcome variables, f^2 is more appropriate than R^2-change, because the latter depends on the total variance accounted for. For interpretation of relevant effect sizes we used the following reference values: small effect ($0.01 \leq f^2 < 0.10$), moderate effect ($0.10 \leq f^2 < 0.33$), and large effect ($f^2 \geq 0.33$).[11] In addition, to determine whether the effects for gender, CHD, and impaired hearing on the outcome variables were equal for both groups of RRTI, the influence of interaction terms were assessed by hierarchical regression analyses. For this purpose, cross-products were computed between RRTI (plus or minus) and, respectively, gender, CHD, and impaired hearing. These cross-products were added as an extra step to the regression equation (which included all main effects). Although asthma was significantly more reported in $RRTI^+$, this subgroup was too small for further analysis.
Power analysis showed at least 137 patients per group were needed to detect a 3-month difference in developmental delay (power 80%, alpha 0.05). All analyses were performed by SPSS for Windows 17.0; statistical significance was defined as a two-sided $p<0.05$.

Results

Patient characteristics and confounding factors

The data on patient characteristics and potential confounding factors are presented in Table 6.1. In total, 531 children with DS aged 8 years were invited to participate; which holds 78% of all estimated living 680 children of this birth cohort in the Netherlands (based on an 84% survival rate).[12] A total of 380 parents (72%) agreed to enroll and 337 children provided data for this study (response rate: 63%). Based on the estimated incidence of DS, our study group represents approximately 48% of all children with DS in this age-cohort in the Netherlands.[1,2,13] In our study, the prevalence of CHD, impaired hearing, eye disease, a diagnosis of asthma and thyroid disease is in accordance with population-based studies in DS.[1,14-16] Not all data could be collected for each patient because of practical problems to plan a home visit for psychological testing at the age of 8 years and/or incomplete returned questionnaires.
The presence or absence of RRTI is reported by parents for 325 (96% of 337) children; in 149 of these children RRTI are present ($RRTI^+$-group) and in 176 children RRTI are absent ($RRTI^-$-group). There is no difference between the $RRTI^-$ and $RRTI^+$ children in proportion of males (p=0.09) or mean age (Table 6.1). The mean age for both subgroups is 8 years and 2 months. The educational career is different between both groups: $RRTI^+$ children with DS

are less likely to primarily start with regular education. Also, the level of education of RRTI$^+$ children with DS who do attend a regular school is significantly lower. The educational level of girls is higher compared to boys, as described earlier.[17] This being the case in RRTI$^+$ as well as in RRTI$^-$ children.

The prevalence of CHD, a diagnosis of asthma, and impaired hearing are significantly increased in the RRTI$^+$ group. We found no significant differences in other potential confounding factors between RRTI$^+$ and RRTI$^-$ children (Table 6.1).

Table 6.1: *Patient characteristics and additional morbidity of 8-year-old Down syndrome population in relation to parent-reported presence of recurrent respiratory tract infections (RRTI).*

	RRTI$^+$		RRTI$^-$		Total		Chi square test
	n	(%)	n	(%)	n	(%)	*p-value*
Male	85	(57)	84	(48)	169	(51)	NS
Female	64	(43)	92	(52)	152	(49)	
Age at inclusion* (mean, range, and SD in years)	8.14 (7.8-8.8) ±0.14		8.15 (7.8-9.1) ± 0.16		8.14 (7.8-9.1) ± 0.15		
School attendance							
Ever attended regular education	99	(30)	142	(44)	241	(74)	0.003
Regular education attendance at inclusion	65	(20)	92	(28)	156	(48)	NS
Preschool *(normally age 4-5 years)*	21	(32)^	11	(12)	31	(20)	0.018
First grade *(normally age 6 years)*	33	(51)^	62	(67)	95	(61)	0.010
Second grade *(normally age 7 years)*	11	(17)^	19	(21)	30	(19)	NS
Level of parental education							
Primary or secondary education	24	(7)	31	(10)	55	(17)	NS
Higher secondary education	55	(17)	63	(19)	118	(36)	NS
University education	70	(22)	82	(25)	152	(47)	NS
Being breastfed (>1 month)	57	(18)	60	(18)	117	(36)	NS
Siblings	140	(43)	170	(52)	310	(95)	NS
Childcare (age <4 years)	142	(44)	160	(49)	302	(93)	NS
Additional morbidity^0							
Congenital heart disease	73	(49)	64	(36)	137	(42)	0.022
Diagnosis of asthma	28	(19)	6	(3)	34	(10)	<0.001
Gastrointestinal disease	26	(17)	19	(11)	45	(14)	NS
Eye disease	77	(52)	81	(46)	158	(49)	NS
Impaired hearing	66	(44)	32	(18)	98	(30)	<0.001
Thyroid dysfunction	19	(13)	20	(11)	39	(12)	NS
Diabetes mellitus	1	(<1)	2	(1)	3	(1)	NS
Other morbidity, not specified	43	(29)	38	(22)	81	(25)	NS

* There was no significant difference in age between both groups determined by a *t*-test.
^Percentage out of all children attending regular education.
^{0} Parental reported morbidity.
Abbreviations: RRTI$^+$ – children with recurrent respiratory tract infections, RRTI$^-$ – children without recurrent respiratory tract infections, NS – not significant.

Table 6.2: *Results of multiple regression analyses for scales scores of the McCarthy Scales of Children's Abilities (MSCA) of 8-year-old Down syndrome children with and without parent-reported recurrent respiratory tract infections (RRTI).*

	RRTI$^+$		RRTI$^-$			
	Total (n=130)	Male (n=75) Female (n=55)	Total (n=140)	Male (n=69) Female (n=71)		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Regression coefficient^0 (β)	Effect size$^\wedge$ (f^2)
Verbal	33.06 (19.13)†	29.64 (19.96) 37.47 (17.18)	40.68 (16.18)	37.09 (15.72) 44.11 (16.08)	-7.33**	0.04
Perceptual-Performance	26.76 (16.58)	21.80 (15.84) 33.33 (15.43)	32.34 (14.90)	28.83 (14.87) 35.93 (14.20)	-5.67**	0.03
Quantitative	9.44 (6.80)	7.86 (6.46) 11.44 (6.75)	12.22 (6.57)	10.46 (6.75) 13.93 (5.99)	-2.61**	0.04
Memory	10.74 (7.77)	9.27 (7.69) 12.64 (7.53)	13.94 (7.37)	11.77 (6.31 16.10 (7.77)	-3.12**	0.04
Motor	23.23 (12.57)	20.03 (12.64) 27.47 (11.32)	27.67 (11.78)	24.99 (11.51) 30.25 (11.62)	-4.63**	0.04
General cognitive score	69.30 (40.25)	59.36 (40.22) 82.29 (36.84)	85.24 (34.43)	76.35 (33.60) 94.00 (33.42)	-15.59**	0.04
Developmental age (SD in months)	3 y 8 m (10.91)	3 y 6 m (10.53) 3 y 11 m (10.66)	4 y 1 m (9.58)	3 y 10 m (9.08) 4 y 3 m (9.30)	-4.05**	0.04

Lower scores indicate more impaired development.
* p<0.05, ** p<0.01, *** p<0.001.
^{0} β = unstandardized regression coefficient of the effect of RRTI, correcting for the effect of socioeconomic status, childcare attendance, being breastfed (>1 month), siblings, gender, congenital heart defect, diagnosis of asthma, gastrointestinal disease, eye disease, impaired hearing, and thyroid dysfunction.
^ Effect size (f^2): small effect (0.01-0.10), moderate effect (0.10-0.33), large effect (>0.33).
† Mean scores are presented with standard deviation between brackets.
Abbreviations: RRTI$^+$ – children with recurrent respiratory tract infections, RRTI$^-$ – children without recurrent respiratory tract infections.

Developmental status, behavioral problems and HRQoL

Development of the children, measured by the MSCA was administrated in 270 children (80% of 337); the results are presented in Table 6.2. Mean scale scores on all domains of the MSCA were significantly lower in RRTI$^+$ children versus RRTI$^-$ children. Small effect sizes were found (Cohen's f^2-range: 0.03-0.04). Moreover, in RRTI$^+$ children the mean developmental age was 3 years and 8 months, compared to 4 years and 1 month in RRTI$^-$ children. Thus, the difference in mean developmental age was 5 months. Results of hierarchical regression analysis for developmental age are presented in Table 6.3. In Step 1, the effect of social economic status, childcare attendance, being breastfed and the presence of siblings was found to be negligible (all not significant), whereas male gender has significantly lower developmental age than female gender, adjusted for the effect of the other variables (Step 2). The results of Step 4 showed a significant effect of RRTI on developmental age, adjusted for the effect of all other variables in the model. Furthermore the effect of RRTI is larger than all separate forms of morbidity (Step 3). No interaction effects are present between RRTI and CHD, gender, or impaired hearing.

Table 6.3: *Hierarchical regression analysis of developmental age obtained by the McCarthy Scales of Children's Abilities (MSCA) in 8-year-old Down syndrome children (n=270).*

	ΔR^2	*p*	β step	*p*	β total	*p*
Step 1	0.006					
Socioeconomic status			0.01		0.23	
Childcare			1.16		1.51	
Being breastfed (>1 month)			1.65		1.32	
Siblings			-0.03		-2.66	
Step 2	0.084	***				
Male gender			-6.15	***	-5.90	***
Step 3	0.038					
Congenital heart disease			-2.66	*	-2.17	
Diagnosis of asthma			-2.20		-1.09	
Gastrointestinal disease			-2.73		-2.47	
Eye disease			0.27		0.41	
Impaired hearing			0.87		1.98	
Thyroid disease			-2.25		-2.61	
Step 4	0.031	**				
Presence of RRTI			-4.05	**	-4.05	**

β = unstandardized regression coefficient; β step is the beta for this variable when it was first entered into the equation; β total is the beta for the variable in the final model including all steps. Negative β means lower developmental age due to this variable.
* $p<0.05$, ** $p<0.01$, *** $p<0.001$
Abbreviations: RRTI – recurrent respiratory tract infections

In total, 317 (94%) CBCL questionnaires were completed (Table 6.4). The results showed increased behavioral problems in $RRTI^+$ children on the scales of withdrawn, somatic complaints, social problems, thought problems, and attention problems, corrected for the effect of the confounders. Effect sizes were small (Cohen's f^2-range: 0.01-0.03). Although mean scores for both internalizing and externalizing problems were significantly increased in $RRTI^+$ compared to $RRTI^-$ children, only the effect size for internalizing problems is relevant (Cohen's f^2 0.03). There was no main effect or interaction effect present for gender, CHD, and impaired hearing on any of the determined variables (data not shown).

The TACQOL-PF was completed for 323 (96%) children (Table 6.5). We found a decreased HRQoL in $RRTI^+$ children in 4 of the 7 subscales: the scores for physical wellbeing, motor skills, autonomy, and social functioning were decreased as compared to $RRTI^-$ children, corrected for the effect of the confounders ($p<0.01$). Effect sizes were small (Cohen's f^2-range 0.02-0.03). Mean scores for boys and girls were equal, and no interaction between RRTI and gender or CHD was present (data not shown). A significant interaction effect was found of impaired hearing by RRTI for the scales social problems and negative emotions (*p*-values respectively 0.05 and 0.02). This interaction effect implied that the effect of having RRTI was – for these two subscales – more pronounced in children with impaired hearing, resulting in a lower HRQoL.

Table 6.4: *Results of multiple regression analyses for the Child Behavior Checklist (CBCL) test scores of 8-year-old Down syndrome children with and without recurrent respiratory tract infections (RRTI).*

	RRTI$^+$ (n=145)		RRTI$^-$ (n=172)			
	Mean	(SD)	Mean	(SD)	Regression coefficient^0 (β)	Effect size$^\wedge$ (f^2)
Withdrawn	3.17	(2.91)†	2.02	(2.30)	1.01**	0.03
Somatic complaints	1.68	(2.20)	1.06	(1.60)	0.42	0.01
Anxious/depressed	0.93	(1.34)	0.85	(1.49)	0.06	0.00
Social problems	4.86	(2.10)	3.98	(2.11)	0.05*	0.01
Thought problems	1.48	(1.87)	0.94	(1.43)	0.58**	0.02
Attention problems	7.34	(3.08)	5.81	(3.07)	1.07**	0.03
Delinquent behavior	1.61	(1.58)	1.34	(1.53)	0.23	0.00
Aggressive behavior	8.06	(5.73)	6.62	(5.64)	1.06	0.01
Sexual problems	0.34	(0.83)	0.38	(0.84)	-0.07	0.00
Total score	34.59	(17.77)	26.25	(17.58)	6.40**	0.03
Internalizing problems§	5.72	(4.85)	3.87	(4.15)	1.49**	0.03
Externalizing problems¶	9.67	(6.84)	7.95	(6.81)	1.29	0.01

Higher scores represent increased behavioral problems.
* $p<0.05$, ** $p<0.01$, *** $p<0.001$.
^{0} β = unstandardized regression coefficient of the effect of RRTI, correcting for the effect of socioeconomic status, childcare attendance, being breastfed (>1 month), siblings, gender, congenital heart defect, diagnosis of asthma, gastrointestinal disease, eye disease, impaired hearing, and thyroid dysfunction.
^ Effect size (f^2): small effect (0.01-0.10), moderate effect (0.10-0.33), large effect (>0.33).
† Mean scores are presented with standard deviation between brackets.
§ Combined from the subscales withdrawn, somatic complaints and anxious/depressed.
¶ Combined from the subscales delinquent and aggressive behavior.
Abbreviations: RRTI$^+$ – children with recurrent respiratory tract infections, RRTI$^-$ – children without recurrent respiratory tract infections.

Discussion

We show that parent-reported RRTI is significantly associated with impaired mental and motor development, behavioral problems, and decreased HRQoL in children with DS. The mean developmental age of children with DS in the group with RRTI is 3 years and 8 months. This is 5 months lower compared to the group without RRTI. Hierarchical regression analysis shows that 3.1% of the developmental age is exclusively associated with the presence of RRTI. This is more than the association of CHD with developmental age (2.2%), only gender is more associated (5.9%). Also, behavioral problems and decreased HRQoL are more common in RRTI$^+$ children. Furthermore, school enrollment was less favorable in RRTI$^+$ children.

Table 6.5: Results of multiple regression analyses for the TNO-AZL Children's Quality of Life Parent Form (TACQOL-PF) test scores of Down syndrome children with and without parent-reported recurrent respiratory tract infections (RRTI).

	RRTI$^+$ (n=148)		RRTI$^-$ (n=175)			
	Mean	(SD)	Mean	(SD)	Regression coefficient^0 (β)	Effect size$^\wedge$ (f^2)
Physical wellbeing	26.43	(3.94)†	27.95	(2.88)	-1.02**	0.02
Motor skills	26.96	(4.40)	28.59	(3.32)	-1.35**	0.03
Autonomy	25.42	(3.99)	26.99	(3.06)	-1.33**	0.03
Cognitive functioning	22.71	(3.60)	22.80	(3.50)	0.07	0.00
Social functioning	27.43	(3.74)	28.95	(3.21)	-1.19**	0.03
Positive emotions	14.91	(1.87)	15.18	(1.42)	-0.17	0.00
Negative emotions	11.50	(1.98)	11.90	(1.99)	-0.27	0.00

Higher scores represent better health related quality of life.
* p<0.05, ** p<0.01, *** p<0.001.
^{0} β = unstandardized regression coefficient of the effect of RRTI, correcting for the effect of socioeconomic status, childcare attendance, being breastfed (>1 month), siblings, gender, congenital heart defect, diagnosis of asthma, gastrointestinal disease, eye disease, impaired hearing, and thyroid dysfunction.
^ Effect size (f^2): small effect (0.01-0.10), moderate effect (0.10-0.33), large effect (>0.33).
† Mean scores are presented with standard deviation between brackets.
Abbreviations: RRTI$^+$ – children with recurrent respiratory tract infections, RRTI$^-$ – children without recurrent respiratory tract infections.

Since RRTI are often accompanied by impaired hearing, specifically verbal skills could be more influenced compared to perceptual-performance, quantitative, memory and motor development in RRTI$^+$ children with DS. In our sample, impaired hearing was indeed more common in RRTI$^+$ compared to RRTI$^-$ children (44% vs. 18%, p<0.001). However, RRTI$^+$ children had lower scores on all developmental scales, with equal effect sizes (f^2=0.03-0.04), and no interaction between RRTI and impaired hearing was observed. So, although hearing loss is a common problem in RRTI$^+$ children with DS, other domains of development are equally decreased compared to the development of verbal skills. In other words, hearing loss does not lead to selective decrease of verbal skills nor does it enhance developmental delay of RRTI$^+$ children, and so does not seem to be a confounder that explains both RRTI and increased developmental delay.

Although RRTI$^+$ children have decreased scores on mental development in the MSCA-test, the TACQOL cognitive functioning subscore is equal in both groups. This means that decreased levels of mental development do not lead to a decreased HRQoL subscore related to cognitive functioning. An explanation for this may be that RRTI$^+$ children are, according to the results of our study, more likely to attend lower levels of education; maybe they fit in better with their classmates, resulting in a better HRQoL subscore related to cognitive functioning in these children.

The parents more often reported the diagnosis of 'asthma' in the RRTI$^+$ children. Although wheezing is a common feature in young children with DS,[4] the overall incidence of asthma

in adults and children with DS is decreased compared to the general population.[5,15,18-20] Therefore, it is doubtful whether these children really suffer from asthma. Additionally, in DS total and specific IgE-values are decreased compared to controls, and there is no increased prevalence of positive skin prick tests.[21-23] Therefore, the symptoms of wheezing and dyspnea in young children with DS are probably caused by mucosal swelling in constitutionally smaller airways during respiratory tract infections, and not attributable to asthma. Since the subgroup of children with DS with parent-reported 'asthma' was small, no separate effect sizes could be determined.

Strengths of this study include the large sample size and the consistency of the age level of all children (all studied at 8 years). Also, independent test assistants administrated the psychological tests. However, parental report is used to classify the presence or absence of recurrent airway infections, which is a methodological limitation of our study. In this way 46% of the children were classified with RRTI, which is a comparable proportion to a recent national health survey where parents reported 38% of children with DS aged 6-10 years as having had a head or chest cold in the previous two weeks.[15] Also, our data are in accordance with earlier studies regarding the overall incidence of CHD,[1,16] and the co-occurrence of hearing impairment in RRTI^{+} children with DS, which were also based on parental report in our study.

For a first exploration of the association between RRTI and development, behavioral problems and HRQoL of children with DS parent-reported RRTI may suffice to attract attention to the potential importance of this frequently encountered problem. However, further research is needed using medical records and physician-based diagnosis to determine a stricter and probably more validly defined group of children as suffering from RRTI.

Many variables that influence development, behavior, and HRQoL – like gender and CHD – cannot be changed, where RRTI potentially can. Therefore, it is important to investigate whether the observed association is based on a causal relationship. If so, better prevention of RRTI might lead to improved functioning in these children. Several causes for RRTI in DS have been proposed, such as hypotonia and (micro)aspiration. Other causes include anatomical abnormalities and different physiology of the respiratory tract including ear, nose, and throat. More frequent (chronic) ear disease, rhinorrhea, sinusitis, and obstructive sleep apnea have all been described in DS and are related to impaired hearing.[24] The co-occurrence of RRTI and impaired hearing in DS has been described before,[25] and is confirmed by our data. This study also shows that the negative effects of the association between RRTI and the HRQoL scales social problems and negative emotions is increased if these children also have impaired hearing. Probably, impaired hearing influences verbal skills, attention, and social functioning negatively. Therefore, periodic surveillance and active treatment by an ENT-specialist could be important for children with DS.

Although CHD is a potential risk factor for hospitalization during respiratory tract infections in children with DS,[26,27] it has not been described as a cause for RRTI in earlier studies. In this study, CHD is significantly more common in the RRTI^{+} children, but there is no significant effect of CHD on development, behavior, and HRQoL additional to the effect of RRTI.

Impairment of the immune system in DS has been described, and has been related to an increased infection rate.[28-30] Most studies involve development and function of T-lymphocytes.[28] B-lymphocytopenia and decreased response to unconjugated pneumococcal vaccinations are related to RRTI in non-DS patients and have been described in DS as well.[23,31] The level of impairment of the humoral immune system and its contribution to RRTI in DS has not been fully elucidated; more research on this topic is needed.

There are limited studies on pathogens of respiratory tract infections in DS. Present studies mainly report uncommon pathogens or more extreme course of disease.[3] More insight in causative pathogens may lead to specific preventive interventions, i.e. prophylactic antibiotics or additional immunizations.

Conclusion

Parent-reported recurrent respiratory tract infections (RRTI) in children with DS are associated with more impaired development, behavioral problems and HRQoL. Therefore, further studies should focus on the question whether this is a causal relationship. If so, better prevention of RRTI in children with DS might stimulate development, prevent behavioral problems, improve HRQoL and enable better school enrolment.

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