

Respiratory tract infections and voice quality in 4-year-old children in the STEPS study

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Summary: Objectives. Health-related factors are part of the multifactorial background of dysphonia in children. Respiratory tract infections affect the same systems and structures that are used for voice production. The purpose of this study was to investigate if the number of respiratory tract infections or the viral etiology were significant predictors for a more hoarse voice quality.

Methods. The participants were 4-year-old children that participated in the multidisciplinary STEPS study where they were followed up from pregnancy or birth to 4 years of age. Data was collected through questionnaires and a health-diary filled in by the parents. Part of the children were followed more intensively for respiratory tract infections during the first two years of life and nasal swab samples were taken at the onset of respiratory symptoms. Our participants were 489 of these children who had participated in the follow-up for at least one year and for whom data on respiratory tract infections, and data on voice quality were available.

Results. The number of hospitalizations due to respiratory tract infections was a significant predictor for a more hoarse voice quality. Neither the number of rhinovirus infections nor the number of respiratory syncytial virus infections were statistically significant predictors for a more hoarse voice quality.

Conclusions. Based on our results, it would be motivated to include questions on the presence of respiratory tract infections that have led to hospitalization in the pediatric voice anamnesis. Whether the viral etiology of respiratory tract infections is of importance or not requires further research.

Key words: children; voice quality; respiratory tract infections; virus; STEPS study

Introduction

The dysphonia prevalence estimates from past studies have varied between 0.12 % [1] and 23.9 % [2]. The etiology is multifactorial and factors that in previous studies have been connected to dysphonia are health related factors [3, 4, 5], personality traits [6, 7, 8], and environmental factors [9, 10, 11, 12]. In this study, focus will be on respiratory tract infections as potential risk factors for a hoarse voice quality.

In adults, more women than men are diagnosed with dysphonia and laryngeal pathologies [13, 14, 15], but for pre-pubertal children, the gender distribution is reversed [8, 15, 16, 17, 18]. The most common laryngeal diagnosis for children with dysphonia in a treatment seeking population studied by Garcia Martins et al. [15] was vocal nodules, followed by vocal cysts, and acute laryngitis. They attribute this to vocal overuse and high-intensity voicing with effort in children. For adults, the most common diagnoses were slightly different for different age groups. Most common in younger adults was functional dysphonia, and in adults over 60 years old, presbyphonia was most common. Other common diagnoses in younger adults were nodules and polyps, while Reinke's edema and acid laryngitis were common in adults over 40 [15].

The most frequent upper respiratory tract infections are the common cold, tonsillopharyngitis, and acute otitis media [19]. Lower respiratory tract infections include bronchitis, bronchiolitis and pneumonia. Infection of the larynx (laryngitis) is usually also classified as a lower respiratory tract infection.

Young children have approximately 5-6 respiratory tract infections per year [20, 21, 22] and they are most common in children up to 4 years of age [23]. In a previous study with partly the same participants as in the present study [24], the annual rate of acute respiratory tract infections during the first two years of life was 5.9. Several viruses can cause the common cold, but the symptoms are roughly the same [20]. One of the most frequently found viruses causing respiratory tract infection is rhinovirus [20, 23, 24]. Different viruses that cause respiratory tract infections peak at different times of the year. While rhinoviruses circulate in the community throughout the year with incidence peaks in the fall and spring, respiratory syncytial viruses and influenza viruses are most common in the winter and early spring [23]. The duration of an upper respiratory tract infection varies between 6 to 9 days in a study by Wald, Guerra, and Byers [25]. Day care center attendance increases the risk for

acute respiratory tract infection in children [26, 27, 28]. Day-care attendance is also a risk factor for hoarseness due to the high noise levels present [8, 29].

One common symptom of respiratory tract infection is cough [30] and in 83 % of the individuals, the cough occurs during the first two days of cold symptoms [19]. According to a review by Brignall, Jayaraman and Birring [31] hoarseness is among the symptoms associated with cough. The results of Irwin and Curley [32] showed that in a help-seeking population with cough, 43 % of the patients stated that hoarseness was the reason for them seeking medical help. Coughing involves mechanical forces about ten times larger than the strain that the vocal folds endure during phonation [33].

Respiratory tract infections affect the same systems and structures that are used for voice production and can therefore be hypothesized to have an impact on voice quality. The epithelium of the vocal folds has an important role in vocal health [34], and respiratory epithelial cells are also the primary site of respiratory virus replication [35]. Rhinovirus infection, as well as other respiratory virus infections, leads to increased production of proinflammatory cytokines in the respiratory epithelium and to recruitment and activation of inflammatory cells [36]. Rhinovirus infection disrupts the epithelial barrier function in the airways and makes the epithelium susceptible to bacterial adherence and infection [37]. Infection can also exacerbate the symptoms of asthma [38].

Children with a hoarse voice quality are perceived more negatively by both adults [39] and other children [40]. A hoarse voice quality can also limit the range of leisure activities that the child can engage in and have an impact on the vocational future of the child. This increases the risk of social exclusion for the hoarse child. Because of the possible negative effects that a hoarse voice quality can have, it would be important to know more about the background of hoarseness in children. This knowledge could be used for screening children in risk groups and to advocate allocation of resources for treatment of the health related factors that are associated with a hoarse voice quality.

The purpose of this study was to investigate if the number of respiratory tract infections or the viral etiology were significant predictors for a more hoarse voice quality. To our knowledge, this has not been investigated before in a pediatric population.

Method

The participants were 4 year old children that participated in the multidisciplinary Steps to the Healthy Development and Well-being of Children (the STEPS study) where they were followed starting from pregnancy or birth. The whole cohort group from which the participants were recruited consisted of 9 811 Finnish or Swedish speaking mothers and their

children who were born in the hospital district of Southwest Finland between January 2008 and April 2010 [41]. Of these, the parents of 1 827 children (mothers $n = 1\ 797$, spouses $n = 1\ 658$) decided to participate in the study. Of these participants, 923 children were followed more intensively for respiratory tract infections during the first two years of life and nasal swab samples were taken at the onset of respiratory symptoms or when the child visited the clinic [24]. Of those who were followed more intensively for respiratory tract infections, 489 children filled our criteria: they had participated in the follow-up for at least one year, provided data on respiratory tract infections, and the parents had answered the voice quality question in the 4-year questionnaire.

Data was collected through a systematic follow-up. Parents filled in questionnaires during pregnancy and when their child was 4 months, 8 months, 13 months, 18 months, 24 months, 3 years, and 4 years. The parents documented respiratory tract infections, physician visits, and medications of the child into a diary on daily basis during the first two years of life (for further details, please see Lagström et al. [41]).

The 4-year questionnaire was distributed electronically to the participants and more than 90 % of the respondents chose to answer the electronic version while the rest opted for the paper version. All earlier questionnaires were distributed in paper form. The parents answered questions concerning their child's development, language, health, everyday life and environment. The question concerning voice quality was "What is your child's voice like (when the child is healthy)?" They were asked to rate their child's voice quality on a ten point equal-appearing interval scale where 0, placed on the left hand, was defined as completely clear and 10, placed on the right hand, was defined as very hoarse. The equal-appearing interval scale was used due to the technical properties of the web survey software where the electronic questionnaire was created. Questions on for example time use for a specific activity or the number of persons in the day care group were answered by filling in a number. All other questions were multiple choice questions.

The variable day care attendance from 13 months to 4 years was coded as no (1) or yes (2). If the parent had reported that the child attended day care in a group setting in all five questionnaires that had been filled in between 13 months and 4 years, the variable was coded as yes (2). An acute respiratory tract infection was defined as the presence of rhinitis or cough, with or without fever or wheezing, documented in the diary by parents, or as a diagnosis of an acute respiratory tract infection by a physician. Since the follow-up time varied between participants, the number of observations of the variables listed in Table 1 (except for the variables voice quality and day care attendance) were divided by the follow-up time and given as observations per year to be comparable.

If several nasal samples were collected during continuous respiratory symptoms, the date of a nasal swab taken more than 14 days from the first one was considered as the first day of a new episode; otherwise the duration of an episode was not limited. The nasal swabs were analyzed, as described in more detail in Toivonen et al. [24], by polymerase chain reaction and antigen tests for rhinovirus, respiratory syncytial virus, enterovirus, influenza A and viruses, parainfluenza viruses, metapneumovirus, and adenovirus.

TABLE 1.

Descriptions of the variables that were considered when constructing the model (N = 489). Voice quality was measured at age 4, day care attendance at five occasions between age 13 months and 4 years, and the other variables during the first two years of life. These variables are listed as observations per year

Variable	Data available, n (%)	Distribution of yes/no answers	Mean (SD)	Range	Number of answers with a value > 0
Voice quality	489 (100 %)		1.54 (2.5)	0–10	
Day care attendance from 13 months to 4 years	489 (100 %)	Yes: 59 No: 430			
Number of RTI episodes	489 (100 %)		6.3 (2.6)	0–14.5	487
Rhinovirus infections	468 (95.7 %)		2.1 (1.4)	0–8	439
Respiratory syncytial virus infections	468 (95.7 %)		0.2 (0.3)	0–1.5	146
Enterovirus infections	468 (95.7 %)		0.1 (0.2)	0–1	84
Influenza infections	468 (95.7 %)		0.02 (0.1)	0–0.94	18
Parainfluenza virus infections	468 (95.7 %)		0.1 (0.2)	0–1	46

Human metapneumovirus infections	468 (95.7 %)	0.03 (0.1)	0–1	26
Adenovirus infections	468 (95.7 %)	0.01 (0.06)	0–0.5	7
Number of hospitalizations due to RTI	489 (100 %)	0.04 (0.2)	0–2	31
Number of laryngitis episodes	489 (100 %)	0.1 (0.27)	0–2	67

Note: RTI = respiratory tract infections

IBM *SPSS Statistics* 21 software (IBM, Armonk, NY) was used for the statistical analyses. Since the voice quality data was not normally distributed, non-parametric tests were generally used. A linear regression analysis was used to investigate if gender, daycare attendance from 13 months to 4 years, the number of respiratory tract infection episodes, the number of hospitalizations due to respiratory tract infections, the number of laryngitis episodes, the number of respiratory syncytial virus infections, and the number of rhinovirus infections were significant predictors for a more hoarse voice quality. The variables 2, 3, 4, 5, and 6 in Table 2 were associated with each other, as shown by the significant correlations of the variables 2 and 4, 3 and 4, 4 and 5, and 4 and 6 (see Table 2). Based on this, we decided to do separate analyses for each predictor variable. The linear regression analyses were performed both as univariate, with only one predictor variable, and multivariate, controlling for gender and day care attendance from 13 months to 4 years. Due to the low number of detections, enterovirus, influenza virus, parainfluenza virus, metapneumovirus, and adenovirus infections were not included in the analysis (see Table 1). The skewness value for the distribution of the dependent variable (voice quality) was 2.07 and the kurtosis value 3.59.

TABLE 2.

The correlations (Spearman's rho) between the continuous variables included in the regression analysis.

Variable	1.	2.	3.	4.	5.	6.
1. Voice quality	1					
2. Number of rhinovirus infections	-.079	1				
3. Number of respiratory syncytial virus infections	.064	.060	1			
4. Number of RTI episodes	.060	.532**	.151**	1		
5. Number of hospitalizations due to RTI	.123**	.014	.070	.118**	1	
6. Number of laryngitis episodes	.035	.036	.008	.144**	.070	1

Note: ** $p < .01$, RTI = respiratory tract infections

Permission for the STEPS study was granted by the Ministry of Social Affairs and Health, and the Ethics Committee of the Hospital District of Southwest Finland (2007-02-27). The parents gave a written informed consent and were informed of their right to withdraw from the study at any point. The description of the scientific data file is formulated according to the standards given by the Office of the Data Protection Ombudsman. The data is stored under lock and key in computers at the Turku Institute for Child and Youth Research (CYRI), University of Turku.

Results

The duration of the more intensive follow-up for respiratory tract infections for the 489 participating children varied between 1.06 years and 2 years (Mean = 1.89, SD = 0.25).

The voice quality ratings for the children in the study group were significantly different from those who were not in the study group ($U = 89043.5$, $z = -2.712$, $p = .007$). Those who were not included had a higher rating on voice quality (Mean = 2.03, SD = 2.94) than those who were included (Mean = 1.54, SD = 2.53). The gender distribution in the study group (girls 47.2 %, $n = 231$, and boys 52.8 %, $n = 258$) was similar to the gender distribution of the excluded group (girls 45 %, $n = 182$, and boys 55 %, $n = 222$).

The number of hospitalizations due to respiratory tract infections was a significant predictor for a more hoarse voice quality both independently and when controlling for gender and day care attendance from 13 months to 4 years (see Table 3). The number of hospitalizations due to respiratory tract infections also correlated significantly with voice quality (Table 2). The model explained 1.7 % (univariate) and 1.8 % (multivariate) of the variance (see Table 3).

TABLE 3.

The results of univariate and multivariate linear regression analyses investigating the relationship between the listed variables and voice quality

	Univariate					Multivariate*				
	B	Std error	Beta	p	Adj R ²	B	Std error	Beta	p	Adj R ²
Gender	-.248	.229	-.049	.280	.000	-.245	.229	-.048	.286	.002
Day care attendance from 13 months to 4 years	.468	.351	.060	.184	.002	.464	.351	.060	.187	.002
Number of RTI episodes	.080	.044	.083	.068	.005	.073	.044	.076	.096	.006
Number of hospitalizations due to RTI	1.922	.622	.139	.002	.017	1.866	.623	.135	.003	.018
				**					**	
Number of rhinovirus infections	-.139	.081	-.079	.086	.004	-.139	.081	-.079	.086	.007
Number of respiratory syncytial virus infections	.713	.391	.084	.069	.005	.699	.390	.083	.074	.008
Number of laryngitis episodes	.502	.420	.054	.232	.001	.479	.420	.052	.255	.002

Note: *Controlling for gender and daycare attendance from 13 months to 4 years (yes/no),

RTI = respiratory tract infections

Discussion

In this prospective study, the number of hospitalizations due to respiratory tract infection was a statistically significant predictor for a more hoarse voice quality, both in the uni- and multivariate analysis (see Table 3). Hospitalizations due to respiratory tract infection had a *B* coefficient of 1.866 in the linear regression analysis where gender and daycare attendance were controlled for. This means that for each additional hospitalization, the voice quality scores increased by 1.866 when the other independent variables in the model were held constant. This was the highest *B* coefficient found in the analyses.

Hospitalization is a sign of a severe respiratory tract infection, and it could be the severity of the symptoms, such as cough, or the treatment provided at the hospital that contribute to the hoarseness. Supplemental oxygen is often used in pediatric patients hospitalized for respiratory tract infections and could affect the mucosa of the pharynx and vocal folds. None of the children in this study were intubated or mechanically ventilated and only one of the children was admitted to an intensive care unit when hospitalized for two separate respiratory tract infections.

The common denominator for the factors related to hospitalization mentioned above is that they all cause a disruption of the structure of the epithelial barrier of the vocal folds. If the epithelium is injured by environmental or systemic irritants, lengthy or forceful vocal fold vibrations, or surgical intervention, this can lead to vocal symptoms and pathology [34]. On a cellular level, the damage can be seen as changes in the cellular structure or cellular organization, or as alterations of the junctions that bind the cells together [34]. It is also possible that the hospitalizations due to respiratory tract infections and hoarseness could both be linked to another, unknown, pathogenic mechanism.

The two-year time gap between the end of the respiratory tract infection data collection and the collection of voice quality data calls for a somewhat cautious interpretation of the results. We do not have information on respiratory tract infections between the ages two and four, but can only hypothesize that the amount of severe respiratory tract infections in the first two years might indicate a sensitivity to infections that continues during early childhood. It is also possible that severe respiratory tract infections in the early years, when the mucosa of the vocal folds is still not fully differentiated into the stabilizing layers, could be especially detrimental to the voice.

The viral etiology of the respiratory tract infections was not a significant predictor for voice quality in our analyses. It is, however, likely that we were unable to detect possible associations between viral etiology of respiratory tract infections and voice quality due to the two-year time gap between the end of collection of nasal swab samples and the voice quality

assessment. The effect of the viral etiology could be short-term and not be noticeable after two years. Because of this, the connection between viral etiology and voice quality should be further studied in a population where all the data would be collected during the same period.

Even our best model only explained 1.8 % of the variance. One possible explanation is that voice quality is multifactorial; i.e. that it is affected by many different factors, and that those included in the model were only a few of these. Another possible explanation for the low R^2 is the fact that the distribution of the voice quality variable was positively skewed, meaning that most of the children had a typical, clear voice quality (i.e. a low score). This is what we expect when measuring voice quality in a normal population, but means that there is not a great deal of variance present to explain for the children that score in the lower end of the scale. This, in turn, affects the adjusted R^2 .

In this study, the parents evaluated the voice quality of their own child. If we instead had used perceptual evaluation by trained listeners, the results could have been somewhat different. In a study by Carding et al. [42], there was for example a discrepancy between whom the parents had rated as hoarse and whom the speech language therapist who evaluated the children's voices had rated as hoarse. In the present study, we cannot exclude that such a discrepancy could be present. On the other hand, in our previous research [43], we had a weak, but statistically significant correlation of .155 between the ratings by the parents and the trained listeners. This indicates that we can expect some agreement between the two types of ratings.

In previous studies where the voice quality of children has been perceptually measured on a scale, the visual analogue scale (VAS) has been more frequently used (see e.g. Kallvik, et al. [43] and Sederholm, McAllister, Sundberg, et al. [10]). Due to the technical properties of the web survey software where the electronic questionnaire was created, an eleven point equal appearing interval scale (EAI) was used instead of a visual analogue scale (VAS) for ratings of current voice quality. The data obtained on an EAI is here seen as comparable to a VAS as the VAS also can be regarded as an interval scale [44]. In a study by Ma and Yiu [45] where ratings of voice related activity and participation measurements on VAS and EAI were compared, the results from both scales were comparable. It is, however, possible that the slight differences in the used scales could have an impact on how well the results of the present study can be compared with the results of previous studies.

Based on our results, it would be motivated to include questions on respiratory tract infections that have led to hospitalization in the pediatric voice anamnesis. The number of rhinovirus or respiratory syncytial virus infections were not statistically significant predictors

for a more hoarse voice quality. Whether the viral etiology is of importance or not requires further research.

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