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The ubiquity of asymptomatic respiratory viral infections in the tonsils and adenoids of children and their impact on airway obstruction



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We would like to dedicate the article to Dr. Linda Brodsky (1952–2014) who spent her entire professional life at the Women and Children's Hospital of Buffalo working to improve the lives of children with airway disease. We would also like to acknowledge Dr. Brodsky's contribution to the standardization of tonsil size in airway obstruction.

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Respiratory virus

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ABSTRACT

Background: Airway obstruction due to enlargement of tonsils and adenoids is a common pediatric problem resulting in sleep disordered breathing. The cause for the relatively abnormal growth of tonsils and adenoids is poorly understood.

Methods: Non-acutely ill children undergoing tonsillectomy and adenoidectomy (T&A) for various reasons were enrolled prospectively in a study to determine the frequency of asymptomatic respiratory viral infections in each lymphoid tissue and to relate the number and types of virus to the degree of airway obstruction. Molecular techniques were used to detect 9 respiratory viruses while Brodsky scores and measurements of percentages airway obstruction were used to estimate the degree of airway compromise due to the tonsil and adenoid, respectively.

Results: Viruses were detected in 70.9% of tonsils and 94.7% of adenoids, $p < 0.001$. Adenovirus was the most common virus detected at 71.1%. Adenoids had an average of 2.4 viruses compared to 0.92 for tonsils, $p < 0.001$. Higher Brodsky scores were only associated with EBV in tonsils, $p = 0.03$, while greater percentages of airway obstruction in the adenoids were associated with adenovirus, EBV, corona virus, parainfluenza virus and rhinovirus, $p \leq 0.005$.

Conclusions: Asymptomatic viral infections are common and directly related to the degree of airway obstruction significantly more often in adenoids than tonsils.

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1. Background

Tonsils and adenoids are lymphoid organs located at the entrance way to the respiratory and alimentary tracts. Their location makes them ideal as the first line of defense against inhaled

and/or ingested viruses and bacteria. The list of respiratory viruses known to cause upper airway infections is long and includes such common agents as adenoviruses (AdV), Boca virus, coronaviruses (CoV), enteroviruses (EV), Epstein Barr virus (EBV), human metapneumovirus (hMPV), influenza viruses (InfV), parainfluenza viruses (PIV), respiratory syncytial virus (RSV), and rhinoviruses (RV). Each of these viruses along with cytomegalovirus (CMV), human herpes viruses (HHV) 6–8, herpes simplex virus (HSV), human papilloma viruses (HPV), human parvovirus B19 and polyomaviruses (PoV) have been detected in tonsillar and adenoidal tissues of asymptomatic individuals [1–21]. As many as 97% of tonsils and adenoids reportedly contain a detectable virus

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[7,8,13,18]. Co-infections with multiple types of virus have been observed. Approximately 80% of adenoidal tissues may contain multiple viruses while lower rates have been reported in tonsillar tissue ranging between 59% and 68% [7,8,13,18]. The rate of detection of viruses varies dependent on the diagnostic technique utilized, age of patient, virus type as well as season of year in which specimens were collected. It is almost certain that the number of microbes detected will continue to increase over time with improvements in the diagnostic tools employed. The effects of asymptomatic infections on tonsils and adenoids remain largely unknown.

The present study was designed to compare the frequency of asymptomatic infection with nine common respiratory viruses in the tonsil and adenoid and to determine the effect of asymptomatic infection on airway obstruction in children undergoing elective excision of the tonsil and adenoid.

2. Methods and materials

The study was prospective and approved by the Institutional Review Board. Parents and children above the age of 7 years were fully informed, and they signed consent and assent forms, respectively.

The study began 2/6/13 and was completed 1/21/14. Children between the ages of 1 and 16 years were enrolled by the authors at the Women and Children's Hospital of Buffalo and in their private office outside of the hospital. All surgeries were performed at the Women and Children's Hospital Buffalo. The study was open to children undergoing surgical removal of adenoids and/or tonsils for various reasons, regardless of gender, race or ethnicity. The tonsils were removed by monopolar cautery by two the surgeons and by the microbipolar technique by the third surgeon. In contrast all three surgeons used curettage to remove the adenoids. Children with craniofacial abnormalities and bleeding disorders were excluded. Data recorded included date of birth, gender, height, weight, BMI, weights of tonsils and adenoids and reason for surgery. The diagnosis of obstructive sleep apnea or sleep disordered breathing was a clinical diagnosis; however, the degree of airway obstruction was estimated by the Brodsky scores for the tonsils and percentages of airway obstruction for adenoids. None of the children exhibited symptoms consistent with an acute respiratory illness at the time of surgery.

Palatine tonsils or adenoids were obtained by the surgeons and forwarded to the Pathology Lab where they were weighed and stored at 2–8 °C before being processed by the Virology Lab; all samples were processed in the Virology lab within 24 h of collection. Detection of adenovirus and EBV was initially performed in the Virology Laboratory at the Women and Children's Hospital of Buffalo.

PCR was performed on DNA extracts from the tonsil and adenoid samples using the ABI 7500 Fast Real-Time Taqman PCR System with adenovirus-specific primers (Life Technologies) and probes (eurofins MWG Operon). Primer-BLAST software was utilized to assure primer specificity. Concurrent testing for RNaseP confirmed extraction efficiency and the absence of PCR inhibitors. A previous adenovirus positive respiratory sample, confirmed by DFA (Diagnostic Hybrids D3 Ultra) was extracted and used as a positive control. A nasopharyngeal swab negative for adenovirus was extracted and used as a positive control for RNaseP activity and a negative control for virus assay.

Samples were run in duplicate for both adenovirus and RNaseP. Samples that showed amplification for the target in only one well, or that had a Ct value for the target exceeding 40 cycles were repeated in duplicate. Repeated samples with target amplification curves in at least one well (regardless of Ct value) were considered

positive. Repeated samples with no target amplification curves in both wells, and a valid RNaseP amplification were considered negative. There were no samples lacking RNaseP amplification and therefore no samples reported as inhibited. Further molecular studies were performed in the Laboratory of Viral Diseases at the Wadsworth Center, New York State Department of Health, Albany, New York, with conventional PCR and sequence analysis. The hexon and fiber genes were amplified, bi-directionally Sanger sequenced on an ABI3700 and analyzed using NCBI Blast analysis.

All other respiratory viruses were detected at the Wadsworth laboratory using the eSensor[®] respiratory viral panel kit (GenMark Inc., Freemont, CA.) which detects Influenza A H1 and H3, influenza A H1pdm09, influenza B, respiratory syncytial virus A and B, parainfluenza virus 1, 2, 3, and 4, human metapneumovirus, human rhinovirus, adenovirus B/E and C, and coronavirus 229E, NL63, HKU1 and OC43 [22]. All results from the viral panel kit were confirmed by real-time PCR. In cases where rhinovirus could not be distinguished from enterovirus, it was classified as rhinovirus/enterovirus indeterminate.

Descriptive characteristics for patients were computed. Weights, Brodsky scores and percentages of airway obstruction were used as indicators of organ size. Categorical variables were reported as proportions in percentage and continuous level variables as means. Independent *t* tests were used to assess the relationship of virus frequency to Brodsky scores and percent of airway obstruction. The Brodsky scores were arbitrarily grouped into low scores of 1 and 2 or high scores of 3 or 4. Percent of airway obstruction was similarly grouped into low scores of 50% or less and high scores of greater than 50%. The independent *t*-test was used to assess the association between low and high Brodsky scores and nine virus types. The independent *t*-test was used to assess the association between low and high percentages of airway obstruction and the same nine viruses. The chi-square test was used to assess the association between the number of virus types and the Brodsky scores and the percentages of airway obstruction. Paired *t*-test was used to assess differences between the number of virus types between tonsils or adenoids. Pearson correlation was used to assess the association between age and total virus number types present. The association between age and total number of virus types was assessed by Pearson correlation. Analysis of variance was used to assess the association between Brodsky score and percent airway obstruction with the weights of tonsils and adenoids, respectively. All statistical tests were assessed assuming two-tailed hypotheses and with alpha of 0.05. All analyses were conducted with SYSTAT 13 (SYSTAT Software, 2004).

3. Results

Fifty-nine children were enrolled in the study ranging in age between one year and 16 years with a mean of 6.2 years. There were 35 females (59.3%). The BMI ranged from 12.9 to 49.4 kg/square meter with a mean of 17.4; 14 (23.7%) children were classified as either obese (eight) or overweight (six). Thirty-eight (62.7%) children underwent surgery for sleep disordered breathing (SDB), seven of whom developed complications of recurrent or chronic (ROC) otitis media and one with ROC tonsillitis. Twelve children underwent surgery for ROC tonsillitis alone. Four children underwent surgery for ROC adenoiditis with tonsillitis or ROC otitis media. A single patient underwent surgery for chronic adenoiditis. A total of 59 tonsils and 57 adenoids were excised. The mean weights of tonsils and adenoids were 6.7 and 2.0 g, respectively. Fifty-five tonsils and 57 adenoids were available for nucleic acid extraction.

Viruses were detected in 39 of 55 tonsils (70.9%) compared to 54 of 57 (94.7%) adenoids, $p < 0.001$. Multiple viruses were detected in

Table 1
Frequency of detection of viruses in tonsils and adenoids.

Virus types	Tonsil (55)	Adenoid (57)	Total
AdV	16	40*	56
EBV	22	21	43
RV	7	31**	38
PIV	4	18***	22
CoV	0	14*	14
RSV	2	6	8
InfV	0	5	5
EV/RV	1	3	4
hMPV	0	2	2
EV	1	0	1

* Detected significantly more often in adenoids than tonsils $p < 0.002$, ** $p < 0.001$, PIV *** $p < 0.003$ and CoV $p = 0.002$.

nine of 55 tonsils (16.3%) and 41 of 57 (71.9%) adenoids ($p < 0.001$). The number of detectable viruses in adenoids tended to decrease patient age increased ($p = 0.07$, $r = -0.24$) although a similar trend was not observed for tonsils ($r = 0.016$, $p = 0.9$).

Table 1 lists the frequency of detection of each type of virus. Adenovirus was the most common overall, detected in 56 specimens, followed by EBV in 43, RV in 38, PIV in 22 and CoV in 14. AdV was also most commonly detected in adenoids at 71.4%, while EBV was the virus most often detected in tonsils at 40.0%. Coronavirus, InfV and hMPV were not detected in tonsils, whereas EV was not detected in adenoids. In four cases, it was not possible to distinguish EV from RV. Each virus identified in the present study was detected more often in the adenoid than tonsil with the exception of EBV; however, the differences were only statistically significant for adenovirus, rhinovirus, parainfluenza virus and coronavirus (Table 1). Coronavirus, InfV, hMPV and PIV were only detected in adenoids and never in tonsils.

When adenoviruses, coronaviruses and parainfluenza viruses were typed, some interesting distributions were observed. Among typable adenoviruses, twenty-eight (82.3%) were either type 1 or 2 (Table 2) with similar frequency and distribution in obese and non-obese subjects. A recombinant adenovirus with a type 15/29 hexon gene and a type 9 fiber gene was identified in a 14 year old obese female. Interestingly, two other recombinant adenoviruses were detected in this population, as well as five samples for which the type could only be determined in either the hexon or fiber gene (but not both), making the definitive designation of type or recombinant not possible. Among the four types of coronavirus tested, OC43 accounted for 90%. Among the four types of parainfluenza virus tested, types 2–4 were detected equally while type 1 was undetected.

The relationships between specific virus type or the number of different viruses and the degree of airway obstruction were also assessed. Brodsky scores and virus types are depicted in Table 3. Sixteen of 22 (72.7%) EBV infected tonsils had scores of 3 or 4, $p = 0.03$. While scores of 3 or 4 occurred with other virus groups, their numbers were relatively low in comparison to EBV, with the exception of adenovirus. The proportion of Brodsky scores of 3 or 4 were not statistically different than the proportion with scores of 1 or 2 for any virus group other than EBV. The number of virus types varied from 0 in 19 tonsils to 4 in 1 tonsil with a mode 1 for the entire group. The number of virus groups in tonsils was not significantly associated with the Brodsky score ($p = 0.49$).

The impact of viral infections on airway obstruction in adenoids was very different than that observed in tonsils. Four virus types, PIV, CoV, AdV and EBV were significantly associated with airway obstruction exceeding 50% (Table 4). The proportion of airway scores greater than 50% varied from 80.9% for EBV, $p < 0.001$ –94.4% for PIV, $p < 0.001$. The number of virus types varied from 0 in 3 adenoids to 7 in 1 adenoid with a mode of 2 for the entire group. As with tonsils, the number of virus types was not significantly associated with the percent of airway obstruction ($p = 0.22$).

4. Discussion

The present report documents the exceedingly high rate of asymptomatic viral respiratory tract infections in the adenoids and tonsils of children undergoing elective tonsillectomy and adenoidectomy. The detection of AdV and EBV in tonsils and adenoids was to be expected. Both are DNA viruses that possess the ability to establish a latency in lymphoid tissue. Adenovirus remains latent predominantly in T lymphocytes while EBV remains latent predominantly in B lymphocytes [11,23]. Lymphocytes latently infected with adenovirus can evade destruction by internalizing surface receptors recognized by the immune cells of the surveillance system [24]. The infection state of the virus remains unclear but is presumably chronic or latent given the high rate of detection of non-replicating virus and the absence of symptoms [1,8,15,25]. Latency in large DNA human pathogenic viruses has been associated with latency-associated transcripts and other evidence of a different replication state to either symptomatic or asymptomatic infections. Such investigations were beyond the scope of the present study.

There are more than 60 types of adenovirus belonging to 7 species classified as A–G [26]. Types 1 and 2 belong to species C and are among the most common adenoviruses known to infect young children [25,27] as was also found in the current study. Additionally, types 1 and 2 have the ability to produce latent infections [25].

Table 2
Typing of adenoviruses from adenoids and tonsils based on hexon and fiber sequences.

Hexon type	Fiber type	Adenovirus type designation	Adenoid	Tonsil	Total
1	1	1	8	4	12
1	No sequence	Uncertain	1	0	1
No sequence	1	Uncertain	3	0	3
2	2	2	9	2	11
2	No sequence	Uncertain	4	2	6
No sequence	2	Uncertain	1	0	1
2	5	H2/F5 recombinant	1	0	1
2	6	H2/F6 recombinant	1	0	1
5	5	5	2	1	3
8	No sequence	Uncertain	1	0	1
15/19	9	H15/29/F9 recombinant	1	0	1
No sequence	No sequence	Not available	5	3	8
Total			37	12	49

Table 3
Correlation of Brodsky score and virus detected.

Virus type	Brodsky score				Total
	1	2	3	4	
EBV*	3	3	11	5	22
AdV	0	6	7	3	16
RV	0	2	3	2	7
PIV	0	1	2	0	3
RSV	0	1	0	1	2
EV	0	0	1	0	1
EV/RV	0	0	0	1	1
CoV	0	0	0	0	0
InfV	0	0	0	0	0
hMPV	0	0	0	0	0
Total	3	13	24	12	52

*P = 0.03.

Table 4
Correlation of obstruction score and virus type.

Virus type	Percent obstruction				Total
	0–<25%	25–<50%	50–<75%	≥75%	
AdV *	2	5	13	19	39
RV *	1	3	10	17	31
EBV **	0	4	6	11	21
PIV *	1	0	6	11	18
CoV ***	1	0	4	9	14
RSV	0	0	3	3	6
InfV	0	0	0	5	5
EV/RV	0	0	1	2	3
hMPV	0	0	1	1	2
EV	0	0	0	0	0
Total	5	12	44	78	139

*p < 0.001, **p < 0.005, ***p = 0.001.

The current study also noted the presence of three and possibly more recombinant adenoviruses. An unusual recombinant adenovirus, H15/29/F9, similar to type 56, was identified in one of the obese subjects. This adenovirus represented a recombination of species D types, the only non-C species adenoviruses in the entire study population. Two other recombinant viruses were identified and for five additional samples, the presence of recombinant elements in the genome could not be determined. Another species D adenovirus, type 36, has been linked to obesity in humans [28]. However, HAdV36 was not identified in any of the 10 obese subjects in the present report.

The second major observation of the present study documents the relationship between the presence of specific viruses and airway obstruction. In tonsils, the presence of EBV was associated with higher Brodsky scores and in adenoids, the presence of PIV, CoV, AdV or EBV was associated with greater percentages of airway obstruction. Higher detection rates of viruses in hypertrophied tonsils and adenoids compared to non-hypertrophied tonsils and adenoids from children has been documented in several other reports [13,21]. The present study provides substantial evidence suggesting that chronic stimulation of both tonsils and adenoids is associated with obstructive airway disease in a quantitative manner. The actual number of different viruses in obstructive tonsils and adenoids remains unknown but is most certainly greater than those identified in the present or previous reports. The current study was limited by the number of microbes tested as well as by the number of children enrolled. Also, the absence of age-matched controls without adenoidal or tonsillar disease makes

the interpretation of the findings in this report, as well as in other studies, more complicated. Future studies should explore the mechanisms underlying the persistence of asymptomatic viral infections in tonsils and adenoids in individuals with and without airway obstruction.

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