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ORIGINAL ARTICLE

Frequency of Common Viruses in Etiology of Acute Respiratory Tract Infections

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Abstract
Objective To determine the frequency rate of *C. pneumoniae*, rhinovirus, respiratory syncytial virus (RSV), influenza virus, metapneumovirus, adenovirus', parainfluenza virus and coronavirus in acute respiratory tract infections in children.
Methods One hundred nine pediatric patients having respiratory tract infections were included in this study. Real time PCR, DFA and cell culture method were used for detection of *C. pneumoniae,* RSV antigen and influenza virus respectively. Multiplex PCR was used for detection of other viruses.
Results No *C. pneumoniae* DNA was detected in the samples. Virus was detected in 43 cases from larynx swabs (43/109, 39.4 %). The frequency order of the viral agents detected were as follows; rhinoviruses 14.7 %, RSV B 7.3 %, influenza A 6.4 %, metapneumovirus 3.6 %, adenovirus 3.6 %, coronavirus 0.9 %, parainfluenzavirus type 3, 0.9 %, parainfluenzavirus type 4, 0.9 % and RSV A 0.9 %. Sensitivity of the PCR and DFA methods for the diagnosis of RSV infections were detected as 100 % and 100 %, respectively. Specificity of the PCR and DFA methods for RSV infections were detected as 97 % and 100 % respectively. Sensitivity of the PCR and cell culture methods for influenzavirus infections were detected as 100 % and 100 %, respectively. Specificity of the PCR and DFA methods for RSV infections were detected as 96 % and 100 % respectively.
Conclusions Prevalence of viral agents was detected as 39.4 %. Influenza viruses and RSV were common. Metapneumovirus was also frequent (3.6 %). *C. pneumoniae* was not found to be a common agent for acute respiratory disease in children.

Keywords Children · *Chlamydophila pneumoniae* · Viral agents · Respiratory tract infections

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Introduction

Acute respiratory tract infections (ARTI) occur frequently in the society [1]. Especially children appear to be at risk. Most of the viruses are transmitted through respiratory droplets. While some of them can stay localized in the respiratory tract, some can show systemic dissemination. In two third of the ARTI, influenza virus and respiratory syncytial (RSV) virus, parainfluenzavirus, adenovirus, coronavirus and rhinovirus are responsible. Influenza is a major cause of morbidity and mortality in infants [2]. Parainfluenza viruses (PIV) are mostly seen in the lower respiratory tract infections of the children after RSV infection. Type 3 is common and approximately half of the children are infected in the first year after the birth. Adenovirus infections are endemic and cause infections mostly in the school ages; 50 % of these infections are asymptomatic. Infections with coronavirus is seasonal and is especially seen in the winter months. The infection caused by rhinovirus is seen throughout the year [3]. Metapneumovirus infections, like RSV infections are common in children younger than 2 y [4]. RSV

infections are among the most important agents causing acute bronchitis and pneumonia in Turkey as in the world. Almost all of the children younger than 3 y may be infected with RSV [5]. *C. pneumoniae*, is responsible for 10–20 % of community-acquired atypical pneumonia in the childhood, 10 % of the acute bronchitis and 5–10 % of the pharyngitis cases [6].

The authors aimed to evaluate various agents causing ARTI in children for the first time in Turkey. This will help in making early viral diagnosis and prevention of unnecessary antibiotics usage and also early initiation of antiviral treatment in high risk group patients.

Material and Methods

A total of 109 children (62 boys and 47 girls) with ARTI findings such as fever, fast breathing, wheeze, cough, nasal draining and nasal congestion between the age group 0–6 y were included in this study which was conducted from January 2006 through June 2007. 46.5 % of the cases were between 6–23 mo, 27.9 % were between 60–72 mo, 18.6 % were between 24–59 mo and 6.9 % were between 0–5 y. Children having any underlying disease were excluded. The complaints and clinical findings of the patients were recorded by a pediatrician designing a questionnaire for the purpose of gathering information.

To obtain *C. pneumoniae* DNA, swab samples were tested by a real time PCR kit (Roboscreen, Germany). ID-Tag™ RVP (Respiratory Viral Panel) kit was used for influenza A (H1,H3,H5), influenza B, RSV (type A, type B), coronavırus (229E, 0C43, SARS, NL63, HKU1), parainfluenza virus, metapneumovirus, rhinovirus and adenovirus [7–9]. This kit was designed as multiplex PCR assay.

For influenza virus, cell culture method [Madine Darby Canine Kidney (MDCK) cells in the epiteloid nature] was preferred as the "Gold Standard". The single-layer MDCK cells were washed with serum free medium and material inoculation was performed. It was incubated for 3 d in 5 % $C0_2$ environment.

RSV antigen was investigated by direct fluorescent antibody (DFA) test (Monofluo screen, BioRad, France). The upper supernatants of the cultures were tested by immunocapture ELISA in terms of influenza A and B.

Results

The order of symptoms were as follows; nasal draining (100 %), cough/nasal congestion (90.6 %), fever (86 %), labored breathing (27.9 %) and stomach pain (4.6 %) and anorexia (6.9 %) (Table 1).

Table 1 Distribution of the detected viral agents according to the symptoms

Symptoms	Influenza A n (%)	Influenza B n (%)	ADV n (%)	RSV A n (%)	RSV B n (%)	PIV-3 n (%)	PIV-4 n (%)	Metapneumovirus n (%)	Rhinovirus n (%)	Coronavirus n (%)	Total n (%)
Cough	7 (100)	3 (100)	4 (100)	1 (100)	8 (100)			4 (100)	12 (75)		39 (90.6)
Nasal draining	7 (100)	2 (66.6)	4 (100)	1 (100)	8 (100)	1 (100)	1 (100)	4 (100)	14 (87.5)	1 (100)	43 (100)
Nasal congestion	7 (100)	3 (100)	3 (100)	1 (100)	8 (100)	1 (100)	1 (100)	4 (100)	10 (62.5)	1 (100)	39 (90.6)
Fever	7 (100)	1 (33.3)	4 (100)	1 (100)	7 (87.5)			4 (100)	13 (81.25)		37 (86)
Labored breathing				1 (100)	7 (87.5)			2 (50)	2 (12.5)		12 (27.9)
Anorexia	1 (12.5)								2 (12.5)		3 (6.9)
Phlegmy cough					1 (12.5)						1 (2.3)
Stomach pain				1 (100)	1 (12.5)						2 (4.6)

PCR Method

The detected virus ratios were 62.7 % and 37.2 % in boys and girls, respectively by PCR multiplex method. According to the study results; *C. pneumoniae* DNA was found negative in all samples by PCR method. Viruses were detected in 43 (39.4 %), of the 109 children's swab samples. The virus detection ratios by PCR multiplex method (with DFA only for RSV A and RSV B, cell culture only for influenza A and influenza B) were as follows; rhinoviruses: 16 (14.7 %), RSV:B 11 (10.1 %), influenza A: 8 (7.3 %), metapneumovirus: 4 (3.6 %), adenovirus: 4 (3.6 %), coronavirus: 1 (0.9 %), parainfluenzavirus type 3: 1 (0.9 %), parainfluenzavirus type 4: 1 (0.9 %) and RSV A: 1 (0.9 %) (Table 2).

Viruses were detected in 43 samples; the most frequently detected virus was rhinovirus with 16 patients (37.2 %). This was followed by RSV B (25.6 %) and RSV type B was detected in 11 patients by the PCR method (Table 3).

In the third order of frequency, influenza A virus was found in 8 of the patients and they were identified as influenza A H3 by PCR. Influenza B was found positive in 3 patients (Table 4). Metapneumovirus was detected in four patients. (9.3 %) and adenovirus in four patients (9.3 %), coronavirus in one patient (2.3 %), parainfluenzavirus type 3 in one patient (2.3 %), parainfluenzavirus type 4 in one patient (2.3 %) and RSV A in one patient (2.3 %) (Table 2).

No statistically significant difference was found between the boys and girls in terms of isolated viruses ($p>0.05$).

Table 2 Ratios of the viral agents detected in cases according to the DFA(only for RSV A and RSV B), cell culture(only for influenza A and influenza B) and multiplex PCR methods

Agents	Boys	Girls	% (n:109)
Rhinovirus	10	6	14.7 %
RSV B[a]	5	3	7.3 %
Influenza A[b]	5	2	6.4 %
Metapneumovirus	2	2	3.6 %
Adenovirus	2	2	3.6 %
Coronavirus	–	1	0.9 %
Parainfluenza 3	1	–	0.9 %
Parainfluenza 4	1	–	0.9 %
RSV A	1	–	0.9 %
Influenza B[c]	–	–	0 %

[a] RSV B antigen of 8 patients were detected by DFA method but RSV B was detected in 11 patients by multiplex PCR. The authors RSV B positive cases in both DFA and multiplex PCR methos as 8

[b] Influenza A was detected in 8 patients by multiplex PCR but only 7 of these 8 patients were detected as positive by cell culture method. We used Influenza A positive cases in both multiplex PCR and cell culture methods as 7

[c] Influenza B was detected in 3 patients by multiplex PCR method but no influenza B was detected by cell culture

Table 3 Comparison of the detected RSV by PCR and DFA methods

Number of patients	PCR	DFA	PCR + DFA
109	11 RSV B	8 RSV B	8 RSV B
109	1 RSV A	1 RSV A	1 RSV A
Sensitivity (%)	100	100	
Specificity (%)	97	100	
Total, n (%)	12 RSV (11 %)	9 RSV (8.2 %)	9 RSV (8.2 %)

RSV type B was detected in 11 patients by the PCR method and RSV antigen in eight of these 11 patients was also positive by the DFA method

Statistical comparisons between groups were made using Chi square or Fisher's exact tests.

Cell Culture Method

Influenza A H3N2 (16.3 %) was identified in the cell culture of seven of patients. No influenza B virus was detected in the cell culture.

Immuno-Fluorescence Method

RSV B and RSV A were detected positive in 8 and 1 patients by the DFA method, respectively.

Sensitivity of the PCR and DFA methods for the diagnosis of RSV infections were detected as 100 % and 100 %, respectively. Specificity of the PCR and DFA methods for the diagnosis of RSV infections were detected as 97 % and 100 % respectively (Table 3). PCR and DFA positivity all together was evaluated as gold standard test. Sensitivity of the PCR and cell culture methods for the diagnosis of influenza infections were detected as 100 % and 100 %, respectively. Specificity of the PCR and DFA methods for the diagnosis of RSV infections were detected as 96 % and 100 %, respectively (Table 4).

DFA test positivity together with PCR is considered as gold standard.

RSV B antigen of 8 patients were detected by DFA method but RSV B was detected in 11 patients by multiplex PCR. Influenza A was detected in 8 patients by multiplex PCR but only 7 of these 8 patients were detected as positive by cell culture method. Influenza B was detected in 3 patients by multiplex PCR method but no influenza B was detected by cell culture.

Discussion

The authors evaluated various agents causing ARTI in children for the first time in Turkey. In the literature evaluation, RSV was amongst the most common causative viral agent

Table 4 Comparison of the detected influenza virus by PCR and cell culture methods

Number of patients	PCR	Cell culture	PCR + Cell culture
109	8 Influenza A (H3)	7 Influenza A	7 Influenza A
109	3 Influenza B	–	–
Sensitivity (%)	100	100	
Specificity (%)	96	100	
Total, n (%)	11 Influenza (10 %)	7 Influenza A (6.4 %)	7 Influenza A (6.4 %)

Influenza A H3 was detected as positive in eight patients by the PCR and influenza A H3N2 was specified in the cell culture of seven of these patients. Again when influenza B was found positive in three patients by the PCR, the influenza cultures of these three patients was found negative

of pneumonia causing bronchiolitis in children younger than 2 y. The second viral agent was parainfluenza type 3 virus which causes pneumonia [5].

Cruz-Canete et al, [8] reported influenza A positiveness as 11. 3 % in 203 pediatric patients under 5 y by PCR. In an another study by Ciblak et al, [10] 111 (68 %) and 52 (31 %) of the 163 positive samples were identified as influenza A and influenza B, respectively with immunocapture ELISA between 2007–2008 season in Turkey. Carhan et al, [11] also reported that influenza A and influenza B were detected as 16.2 % and 7.6 % in 1157 clinical specimens, respectively. In a study by Akın et al, [7] RSV, influenza A and influenza B were detected in 20, 10 and 6 cases in 91 children with ARTI between the ages 0–19, respectively. In the present study, influenzae A virus was found positive in 7 (6.4 %) and 11 patients (10 %) by the cell culture and PCR methods, respectively. The present influenza A ratio is less than the results of Cruz-Canete et al, [8] and Carhan et al, [11]. Influenza B was detected in 3 patients by multiplex PCR but no influenza B was detected by cell culture; these accepted 3 positive cases were accepted as false positive .

In a study performed by Lazzaro et al, [5] with 73 children, RSV was detected as 45 %. RSV was detected as 29.5 % in 98 % of 332 pediatric patients by Kanra et al, [12]. Gökalp et al, [13] detected RSV in 17 (21.35 %) and 26 (32.5 %) of 80 children between 0–24 mo by the cell culture and DFA methods, respectively. In a study performed by Hacímustafaoğlu et al, [14], 83 % of the pregnant women as well as all the babies of these mothers (>20 RU/ml) were anti-RSV IgG positive. In a study performed by Boivin et al, [15] 46 % and 51 % RSV were detected by the real-time PCR method in 204 nasopharyngeal samples of children. Out of 77 samples tested for RSV with DFA, 17 (22.1 %) were found RSV-positive with a mean age of 8.24±7.21 mo in children by Gupta et al, [16]. Of the 126 patients, 46.66 % children were positive for RSV while 58.33 % were negative for RSV between the age of 4–24 mo by Hemalatha et al, [17]. Yeolekar et al, [18] collected nasopharyngeal aspirates from 385 children with acute respiratory tract infections and detected 143 (37.1 %) viral positivity for respiratory viruses. Of the six respiratory viruses, the most common was respiratory syncytial virus (RSV) in 100 (26 %) patients, followed by influenza viruses in 21 (5.4 %), parainfluenza in 8 (2.07 %), adenovirus in 3 (0.8 %). The present RSV results are much less than the results of this study. RSV B was found positive in 8, and 11 patients of 109 pediatric patients by DFA and PCR methods, respectively in the present study. RSV A was found positive in one patient by both DFA and real time PCR methods.

The real frequency of metapneumovirus infections in children is not known. During the winter months of the year 2000, according to the prospective follow up study results performed in Holland and Finland, metapnemovirus was detected in 9–10 % cases of the children with the inexplainable respiratory tract infection findings or acute wheezing [19, 20]. The infection ratio in the infants at the age of 7–12 mo (31 %) was more frequent than that of the 0–6 mo of children (19 %) in United States of America [6]. Yahia et al, [21] detected 8 % metapneumovirus in nasopharyngeal aspirates of 600 infants and children with respiratory infections. They also stated that the rate was significantly higher among children aged 2–24 mo compared to other age groups. In the present study, metapneumovirus was detected in four pediatric patients (3.6 %). The present results for metapneumovirus are in concardance with study results of Yahia et al, and other studies. Three of the present cases were in the 6–23 mo age range and one patient was in 24–59 mo age range.

Xie et al, [22] investigated the viral pathogens of ARTI in 1914 (1281 male and 709 female) children of different age groups and outlined the epidemic feature of different viruses by reverse transcription PCR method. They found the positive rate of rhinovirus as 36.2 % in group of <1 y old. Xiao et al, [23] detected viruses in 871 samples (74.76 %), among which RSV (27.03 %) was the most common virus, followed by human rhinovirus (17.33 %) in 1165 hospitalized children with ARTI. They stated the highest positive rate was noted in the age group of 6 mo to 1 y and concluded that viral infection-associated acute respiratory tract infection shows a prevail in the age group of 6 mo to 1 y in winter as well. Vidaurreta et al, [24] reported that rhinovirus was

the most frequent followed by respiratory syncytial virus in children <5 y old with acute respiratory infections. Viral diagnosis was achieved in 81 % hospitalized and 57 % of outpatients in their study. They concluded that the use of viral diagnostic techniques allowed the identification of an etiologic agent in most of the hospitalized patients and more than half of outpatients. The addition of RT-PCR for rhinovirus, allowed the identification of this etiologic agent. The authors found the rhinovirus rate as the highest (14.7 %). The present result are in concordance with the study results of Vidaurreta et al, [24] Xie et al, [22] and Xiao et al, [23]. The authors also detected 7 (43.7 %) rhinovirus cases of total 16 cases in children under 23 mo old similar to Xie's study positive rate of rhinovirus as 36.2 % in group of <1 y old.

Khor et al, [25] reported a retrospective study with a total of 10269 respiratory samples from all children (less than or equal to) 5 y old with respiratory tract infections received at the hospital's diagnostic virology laboratory between 1982–2008. They reported adenoviruses as (141, 5.2 %) as the forth common virus after RSV (1913, 70.6 %), parainfluenza viruses (357, 13.2 %) and influenza viruses (297, 11.0 %). Zhang et al, [26] investigated the prevalence of respiratory viruses, including respiratory syncytial virus , influenza virus types A and B, parainfluenza virus 1–3, and adenovirus , in 412 hospitalized children. In their study, RSV was detected in 25.0 %, influenza virus types A and B in 19.4 %, parainfluenza 1–3 in 14.6 %, and adenovirus in 4.1 % of the total samples. They also reported that most viral infections occurred in the first 5 y of life, and the incidence of viral infection peaked during early spring and winter. Farshad et al, [27] reported the most commonly detected virus was parainfluenza virus 3 in 32 (15.8 %) cases followed by respiratory syncytial virus 26 (12.9 %); parainfluenza 1 and parainfluenza 2, each 13 (6.4 %); influenza A 16 (7.4 %); influenza B 7(3.5 %), and adenovirus 12 (5.9 %) in 202 hospitalized children (1 mo–5 y) with clinical evidence of ARTI. In the present study adenovirus infection rate was detected as 3.6 %. This was in the forth rank of etiological agents. The present results are in concordance with the results of Khor et al, [25] Zhang et al, [26] and Farshad et al, [27] (5.9 %).

Prill et al, [28] reported that coronavirus was detected in 113 (7.6 %) of 1481 hospitalized children with ARTI. In another study, Al Hajjar et al, [29] reported detections of 8.3 % metapneumoviruses and 2.8 % coronaviruses among 489 specimens from children less than 16 y old by PCR. They concluded that coronaviruses may cause severe ARTI with underlying conditions. Kristoffersen et al, [30] reported 68 (12.7 %) coronavirus in hospitalized Norwegian children with ARTI and concluded that children with coronavirus were older than children with RSV and tended to have chronic disease (other than asthma). Lau et al, [31] reported that 10 (1.6 %) of the 629 children (6 mo–5 y) had coronavirus infection. In the present study, only 1 coronovirus (0.9 %) case was detected and this result is less than other study findings.

Kabra et al, [1] investigated clinical samples of 95 children to identify pathogens responsible for acute severe lower respiratory tract infection in under five children by non-invasive methods (blood culture and serology). They concluded that viruses from nasopharyngeal aspirates could be isolated in 36 (38 %).Khor et al, [25] detected 357 (13.2 %) parainfluenza viruses (type 3) in 10269 respiratory samples from all children with respiratory viral infections (less than or equal to) 5 y old. Xie et al, [22] found the positive rate of rhinovirus as 12 % in group of <1 y old. Ren et al, [32] reported that parainfluenza viruses were detected in 246 (12.2 %) children with ARTI, of whom 25 (10.2 %) were positive for parainfluenza virus 4, 11 (4.5 %) for parainfluenza virus 2, 51 (20.7 %) for parainfluenza virus 1, 151 (61.4 %) for parainfluenza virus 3. The authors detected 1 parainfluenza 3 (0.9 %) and 1 parainfluenza 4 (0.9 %) in children younger than 23 mo old. The present results are not in concordance with the other results. In other words, the present results were much lower than the results of other studies.

The present study is important because it determined the virus frequency and examined various viruses in a single clinical sample in terms of respiratory tract etiology in 0–6 y aged children. ARTI are very common in the society. The number of metapneumovirus infections causing ARTI has recently been increased in the world as in the present study. Rhinoviruses was the most diagnosed viral pathogen among ARTI agents. The present results are in concordance with other epidemiological studies performed in the world.

Conflict of Interest None

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