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Viral Etiology and Symptoms of Acute Upper Respiratory Tract Infections in Children

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Aims: To determine viral causes of acute upper respiratory tract infections and clinical findings in children living in Istanbul, Turkey.

Materials and Methods: This prospective study was carried out in 234 outpatient children (age range: 1-180 months) with acute upper respiratory tract infections, seen in the outpatient clinic at Istanbul Medical School Children's Hospital. After clinical findings were recorded, nasal swab specimens were taken. In 201 specimens collected, influenza-A and -B, adenovirus, respiratory syncytial virus, and parainfluenza viruses were studied using direct fluorescence antibody, polymerase chain reaction (PCR), and cell culture techniques.

Results: Rate of virus isolation was 29.8% (60/201). The viruses isolated in decreasing order were influenza-A (36.6%), adenovirus (28.4%), parainfluenza (14.9%), and respiratory syncytial virus (13.5%). All influenza-A cases were type H3N2. The common viruses in children less than 2 years of age were respiratory syncytial virus (63%) and adenovirus (59%), whereas influenza-A was dominant over 2 years of age (82%). Clinical symptoms did not differ among the different viral causes.

Conclusions: Viral etiologies in children with acute upper respiratory tract infections were shown at a rate of 29.8% and the most common causes were influenza-A, adenovirus and parainfluenza viruses.

Key Words: Child, infection, respiratory, viral

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Çocuklarda Akut Üst Solunum Yolu Enfeksiyonlarının Viral Etiyolojisi ve Klinik Özellikleri

Amaç: İstanbul'da yaşayan çocuklarda akut üst solunum yolu enfeksiyonlarının viral etiolojisinin ve etkenlere spesifik klinik bulgularının saptanması.

Yöntemler: Prospektif, klinik bu araştırma 1-180 ay yaş aralığında olan 234 üst solunum yolu enfeksiyonlu çocukla ayakta yürütüldü. Vakaların klinik bulguları kaydedildikten sonra, nazal sürüntü örneği alındı. Bu örnekte influenza-A ve B, adenovirüs, respiratuar sinsiyal virüs, parainfluenza virüsler direk floresan antikor, PCR ve hücre kültür yöntemleri kullanılarak 201 örnekte araştırıldı.

Bulgular: Virüs izole edebilme oranımız % 29.8 idi (60/201). En sık izole edilenler sırasıyla influenza-A (% 36.6), adenovirüs (% 28.4), parainfluenza (% 14.9), respiratuar sinsiyal virüs (% 13.5) idi. İnfluenza-A vakalarının tümü H3N2 tipindeydi. İki yaş altında en sık respiratuar sinsiyal virüs (% 63) ile adenovirüs (% 59) iken, iki yaş üzerinde influenza-A baskındı (% 82). Klinik bulgular viral etkenlere göre spesifik bir farklılık göstermiyordu.

Sonuç: Çocuklarda üst solunum yolu enfeksiyonlarında viral etioloji % 29.8 oranında gösterilebildi ve en sık etkenler influenza-A, adenovirüs ve parainfluenza virüstü.

Anahtar Sözcükler: Çocuk, enfeksiyon, solunum, viral

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Introduction

The most common infectious disease in children seen in outpatient clinics is acute upper respiratory tract infections; among them the most commonly seen is nasopharyngitis (1). The leading viral causes of upper respiratory tract infections include rhinovirus, influenza virus, adenovirus (ADV), enterovirus and parainfluenza viruses (PIV) (2-4). There are many different serotypes of these viruses, e.g. over 200 types of rhinovirus have been defined (5,6). The newly identified types, like metapneumovirus, are new additions to the list (7). Viral upper respiratory tract infections are especially common in children under 5 years of age; distribution of viral etiology differs by regions

and seasons. The incidence of infections shows an increase in winter and spring. Some of the clinical findings are common, but different findings are observed in different viral etiologies as well. Many of them are considered as bacterial infection and hence antibiotics are utilized unnecessarily (8). Moreover, these viruses may lead to or induce other diseases such as asthma. Viral nasopharyngitis, influenza virus being the most common etiology, is also one of the leading causes of hospitalizations.

The objective of this research was to determine the viral etiology in children with acute upper respiratory tract infections and associated specific clinical findings in an outpatient setting.

There was little information on viral etiology of respiratory infections in Turkish children in the published medical literature (9,10). A PubMed database search did not reveal any published or indexed article that investigated viral causes of upper respiratory tract infections in Turkish children. Therefore, we planned the current study accordingly. Furthermore, we planned to analyze the range of clinical symptoms among the different viral upper respiratory infections with the hope that the results might be helpful to practicing physicians.

Materials and Methods

Location and time of the study: This single center study was carried out in Istanbul, in a university hospital (University of Istanbul, Istanbul Medical School, Pediatric Outpatient Clinic), between the 7-month period from October 1, 2005 to April 30, 2006. Approximately 20,000 patient visits are made to the Pediatric Outpatient Clinic each year. A total of 3,000 patients were seen during the working hours (08.00-17.00) within the study period. Of these, 600 were diagnosed to have acute upper respiratory tract infection. The study included 234 patients (40%) who met the criteria for inclusion in the study and accepted to participate in the study.

Type of the Study: This is a clinical and descriptive study.

Characteristic Features of the Cases

Inclusion criteria

a. Clinical signs related to acute upper respiratory tract infections;

- b. Disease symptoms within the last 7 days;
- c. No known chronic disease;
- d. Voluntary consent to participate in the study;
- e. No hospitalization required;
- f. Absence of findings that could be related to streptococcal infections (sore throat together with high fever, painful cervical lymphadenopathy, exudative tonsillopharyngitis, and petechiae on the soft palate, etc.).

Exclusion criteria

- a. A known chronic disease;
- b. Presence of long-lasting upper respiratory tract infection (longer than 7 days);
- c. Refusal to participate in the study;
- d. Presence of findings related to lower respiratory tract infection, such as dyspnea, cyanosis, tachypnea or pulmonary auscultation findings suggestive of pneumonia;
- e. Hospitalization required;
- f. Presence of findings related to streptococcal infections.

Description of Acute Upper Respiratory Tract Infection

1. Presence of findings that could be related to acute upper respiratory tract infection (watery rhinorrhea, fever, nasal congestion, myalgia, conjunctivitis, cough, hoarseness, etc.).

2. Absence of findings that could be related to lower respiratory tract infection (tachypnea, dyspnea, lung auscultation findings-crepitant rales, cough with sputum, cyanosis, etc.).

Specimen Collection for Viral Analysis

In cases meeting the criteria for inclusion, culture was collected by swabbing superficial mucosal surface deeply on both sides. Culture samples were not collected from nasopharynx via oral approach because that technique is more invasive than obtaining nasal swab. Moreover, nasal swab is known to be effective in the diagnosis of viral upper respiratory tract infection; therefore, nasal swab was preferred (11).

Virus Analysis Methods

After the upper respiratory tract specimen was mixed by vortexing, it was centrifuged at 2000 rpm for 10

minutes. The supernatant was used for isolation of influenza virus, while the cellular component in settlement was used to diagnose parainfluenza, respiratory syncytial virus (RSV) and ADV. For the diagnosis of influenza viruses, live cell culture media were used. For the other viruses, direct fluorescent antibody (DFA) tests were preferred. The Madin-Darby Canine Kidney (MDCK) cells that are of epithelioid nature were used for isolation of influenza virus. Single-layer MDCK cells were washed with culture without serum and then 100 µL material was incubated. After centrifugation at 2000 rpm at less than 34°C and addition of culture without serum that contains trypsin-TPCK, cells were incubated in 5% CO₂ milieu at 34°C for 3 days. At the end of this process, immunocapture ELISA test for influenza-A and -B was used for detection in the supernatants. Supernatants were used to determine viral titration by hemagglutination (HA) test, to determine antigenic type by in-house polymerase chain reaction (PCR) test. Immunocapture ELISA assay was used for anti goat-rabbit immunoglobulin, conjugate peroxidase, ABTS tablet and tampon, poppy monoclonal antibodies, the specific references serum samples for influenza virus type A (H1N1, H3N2), and type. Diluted Coulter over fluid and guinea pig erythrocytes (0.8%) on the U-plaque were used for HA tests. For diagnosis of parainfluenza, RSV and ADV infections, the cell precipitate samples were stained with the monoclonal antibodies, which were marked by virus-specific FITCH, and they were observed under immunofluorescence microscopy. Cells reflecting typical fluorescing green color were accepted as positive for virus (12,13).

Clinical Findings and Follow-up

At the time of the study entry, detailed case histories were taken, physical examinations were done and case forms were completed. Clinical findings of the cases including fever, cough, nasal congestion, watery rhinorrhea, conjunctivitis, and cervical lymphadenopathy were recorded.

Complications and Hospitalization

Development of signs or conditions that were not consistent with acute upper respiratory tract infections such as pneumonia, dyspnea, cyanosis, or middle ear infection were considered as a complication. The incidence of hospitalization was determined via follow up by telephone on the 30th day and the conditions of the

patients who were admitted to our hospital clinics were duly recorded.

Ethical Committee Approval

The study was started after the receipt of the approval of the Ethics Commission, University of Istanbul, and Istanbul Medical School. Signed written consent forms were obtained from the families of the patients. The study was carried out in accordance with the Helsinki Declaration (The Ethic Commission Approval Report No. 544/2004).

Statistical Analysis

The frequencies of qualitative independent variables of the main group were determined. Groupings were made according to etiology. In the evaluation of the qualitative and quantitative parameters, chi-square and Student's t tests were utilized, respectively. Statistical analyses were made by SPSS software program licensed to the University of Istanbul.

Financial Support for the Study

Research was supported by the University of Istanbul, Research Projects Executive Secretariat (Project # 309/0501 2005).

Results

Two hundred thirty-four patients fulfilling the eligibility criteria were included in this study. Patients were clinically evaluated and 234 nasal swab specimens were collected. Viral etiology analyses could be made on 201 specimens (85% of all cases; 201:234). Fifty-seven percent were males. Average age was 53.5 ± 40.9 months (1-180 months), average weight 18.3 ± 9.9 kg (2.4-55 kg), and average height 101.9 ± 25.3 cm (51-165 cm). 5.9% of the cases were between 0-5 months of age, 20.3% between 6-23 months, 35.6% between 24-59 months, and 38.1% older than 60 months. Approximately 26% of the cases were under 2 years of age. The rate of day-care center attendance was 18.9%; flu vaccination rate was 12.4%. Of these vaccinations, 90% were done one year ago. There was active smoking in the household in 47.7% of the cases (Table 1).

Isolated Viruses

Of 201 cases from whom nasal swab specimens were collected, virus isolation was possible in 60 cases (29.8%). The most frequently encountered virus was

Table 1. Characteristics of virus isolated or not-isolated groups (n: 201).

Symptoms	Virus isolated (n:60) n (%)	Virus not-isolated (n:141) n (%)	P
Cough	55 (91.6)	129 (91.4)	NS
Rhinorrhea	52 (86.6)	75 (53.1)	<0.01
Nasal stuffiness	35 (58.3)	87 (61.7)	NS
Fever	34 (56.6)	90 (63.8)	NS
38-38.5 °C	25 (41.6)	67 (47.5)	NS
>38.5 °C	9 (15)	23 (16.3)	NS
Cervical lymphadenopathy	24 (40)	61 (43.2)	NS
Loss of appetite	18 (30)	69 (48.9)	<0.01
Conjunctivitis	15 (25)	32 (22.6)	NS
Abdominal pain	3 (5)	4 (2.8)	NS

NS: not significant.

influenza–A (36.6%). All of the influenza viruses isolated were in group H3N2. The frequencies of other viruses in order were as follows: ADV 28.3%, RSV 13.3%, parainfluenza virus type-1 (PIV-1, 11.6%), parainfluenza type-3 (PIV-3, 3.3%) and influenza–B (1.6%). More than one virus was isolated in 3 cases: influenza-A and ADV in 2 cases, and ADV and RSV in 1 case. The rate of mixed isolated viruses was 4.9% (Table 2).

Viruses Isolated As Per Age Groups

When evaluated according to age groups, 35% of the isolated viruses were collected from breast-fed children below 2 years of age and 65% from those over 2 years of age. The most frequently isolated viruses from the breast-fed children were RSV (63%) and ADV (59%). Our rate of isolation of influenza–A was found as 18%. From the children over 2 years of age, PIV and

influenza–A viruses were the most frequently isolated (100% and 82%, respectively). In this group, RSV frequency was low (27%; Figure 1).

Characteristics of Symptoms and Signs According to Viral Etiology

The prominent symptoms of the cases in which a virus was isolated were cough (91.6%), watery rhinorrhea (86.6%), nasal congestion (58.3%) and fever (56.6%). Cervical lymphadenopathy was observed in 40% of the cases, loss of appetite in 30% and conjunctivitis in 25%. Cough was the leading symptom particularly in patients with RSV infection. Watery rhinorrhea was distributed proportionately in all cause groups, whereas nasal congestion was prominent especially in PIV infections. Conjunctivitis and cervical lymphadenopathy were seen more frequently in influenza–A virus infections. The

Table 2. Distribution of isolated viral agents is shown according to age parameter (n: 201)*.

Age (month)	Influenza-A** n (%)	ADV n (%)	RSV n (%)	PIV-1 n (%)	PIV-3 n (%)	Influenza-B n (%)	Inf-A+ADV n (%)	RSV+ADV n (%)	P	Total n (%)
0-5	-	3 (18)	4 (50)	-	-	-	-	-	< 0.01	7 (11.6)
6-23	4 (18)	7 (41)	1 (13)	-	1	-	1	-	< 0.01	14 (23.3)
24-59	6 (27)	2 (12)	3 (27)	6 (86)	1	1	-	1	< 0.01	20 (33.3)
≥60	12 (55)	5 (29)	-	1 (14)	-	-	1	-	<0.01	19 (31.6)
Total (n) (%)	22 (36.6)	17 (28.4)	8 (13.5)	7 (11.6)	2 (3.3)	1 (1.7)	2 (3.3)	1 (1.6)		60 /201 (29.8)

*: Calculation of ratio was not done due to being only one case. ADV: adenovirus; RSV: respiratory syncytial virus; PIV: parainfluenza virus; Inf: influenza. **: All influenza-A virus types were in H3N2 group.

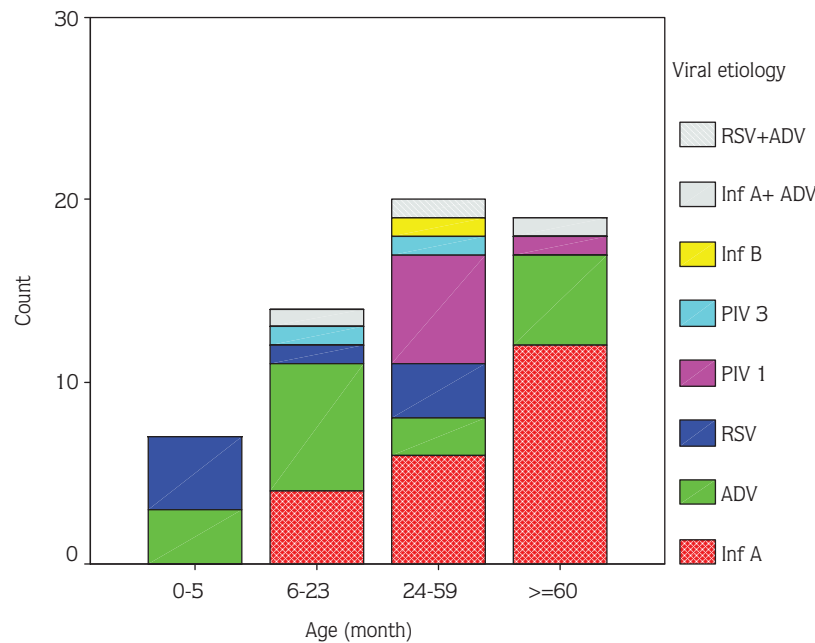


Figure. Distribution of viral agents isolated from nasal swab divided according to age groups (n: 201).
RSV: respiratory syncytial virus; ADV: adenovirus; Inf: influenza;
PIV: parainfluenza virus.

prominent symptoms of influenza–A cases were cough, watery rhinorrhea, fever and cervical lymphadenopathy. In ADV infections, the principal symptoms were cough, watery rhinorrhea and fever. Cough and watery rhinorrhea were the primary symptoms in RSV infections; fever was not a prominent one. Abdominal pain was more common especially in RSV. In PIV infections, like influenza

and ADV, the prominent symptoms were cough, watery rhinorrhea and nasal congestion (Table 3).

Hospitalization and Complications

Complications were seen in 9 cases only (4.4%). They were usually in the 6-59 months of age group (75%). Of these, only 2 were in the group in which viral etiology

Table 3. Distribution of symptoms is shown in the virus-isolated group (n: 60)*.

Symptoms	Influenza-A (n:22) n (%)	ADV (n:17) n (%)	RSV (n:8) n (%)	PIV-1 and -3 (n:9) n (%)	Mixed (n:3) n (%)	Influenza-B (n:1)	P
Cough	21 (95)	15 (88)	8 (100)	7 (78)	3 (100)	1	For RSV, <0.01
Rhinorrhea	19 (86)	14 (82)	7 (87)	8 (89)	3 (100)	1	NS
Nasal stuffiness	10 (45)	10 (59)	5 (63)	7 (78)	2 (67)	1	For PIV, <0.01
Fever	14 (63.6)	10 (59)	3 (38)	4 (44)	2 (67)		
38-38.5 °C	9 (40)	8 (47)	3 (38)	2 (22)	2 (67)	1	For Inf-A and ADV, <0.01
>38.5 °C	5 (23)	2 (12)	-	2 (22)	-	-	
Cervical lymphadenopathy	14 (64)	5 (29)	2 (25)	2 (22)	1	-	For Inf-A, <0.01
Loss of appetite	6 (27)	3 (18)	3 (38)	3 (33)	2 (67)	1	For RSV, < 0.01
Conjunctivitis	8 (36)	3 (18)	1 (13)	2 (22)	-	1	For Inf-A, <0.01
Abdominal pain	1 (4.5)	1 (5.8)	1 (12.5)	-	-	-	For RSV, <0.01

*: Calculation of ratio was not done due to being only one case. ADV: adenovirus; RSV: respiratory syncytial virus; PIV: parainfluenza virus; Inf: influenza.

was known, the isolated cause being PIV. Complications were acute bacterial rhinosinusitis in 3 cases, acute gastroenteritis and persistent vomiting in 2 cases, bronchopneumonia in 2 cases, and facial paralysis (Bell's paralysis) in 1 case. The complication of the case in which PIV was isolated was acute gastroenteritis. Acute middle-ear infection occurred in 1 case. From the nasal swab of the case with otitis media, PIV had been isolated. The number of hospitalized cases was 3 (1.5%) and all were between 6-23 months of age. Virus isolation could not be made in any of the hospitalized cases. Two had bronchopneumonia and one had acute gastroenteritis. There was no mortality in the whole study group.

Discussion

In this study, which was conducted in outpatients with acute upper respiratory tract infections, the rate of virus isolation from nasal swab specimen was 29.8%. This rate is similar to the rates reported in other studies (14,15). Metapneumovirus, a new respiratory tract infection virus, and rhinovirus were not included in the investigated causes of viral etiology. The reasons were that rhinoviruses have many types and technically it is not easy to search them, and further, because our group consisted of outpatients, metapneumovirus was less likely to be a leading cause of infection. However, if these viruses could be studied, the isolation rate might have been higher. The most common isolated viruses were, in sequence, influenza-A (36.6%), adenovirus (28.3%) and parainfluenza viruses (14.9%). RSV was not prominent. We had taken nasal swab specimen; if we had preferred nasopharyngeal aspirates, this rate could have been higher. Mixed viral cause rate was 4.9%. RSV was common especially in children under 6 months of age, whereas ADV and influenza-A were the most commonly isolated causes in the age group of 6-23 months. Influenza-A and PIV were prominent in the 24-59 months of age group. Influenza-A was again highly prominent in the oldest age group of 60 months and higher. In this group, no RSV was detected.

Nasal swab technique was preferred in the collection of the material since it is known that this technique is as good as nasal aspirate in the determination of the causes of upper respiratory tract infections (11). Nasal swab could indicate influenza and other viruses. When taking the swab, nasal mucosa was gently traumatized to enable

us to obtain epithelium. This way of sampling might contribute to the increase of the influenza isolation rate.

Among the symptoms, cough was the most common, followed by watery rhinorrhea, nasal congestion and fever. This is an expected situation in upper respiratory tract infections. The fact that a statistically significant difference among the symptoms according to causes could not be proven supports the hypothesis that a specific etiology cannot be concluded based solely on the clinics of viral infections. However, it was interesting to note that fever was less common in RSV cases, fever and watery rhinorrhea were more common in influenza-A, and nasal congestion was the prominent symptom in PIV. From the symptom point of view, no significant difference was determined between the groups of cases in whom viruses could or could not be detected.

Seventy-eight percent of the children included in our study were under 5 years of age; viral infections were especially common in this group and the time period of the study was a period in which such cases were frequently seen. An interesting and unexpected incident during the study period was that bird flu was seen in Turkey for the first time (16). There was no bird flu case among our patients. All influenza-A viruses isolated were of H3N2 serotype.

The rate of complication was 4.4% and of hospitalization was 1.5%. These were higher than the reported values (17,18). The observed complications occurred in patients with PIV in whom a virus was isolated. Hospitalization was seen especially in children less than 2 years of age. Complications were rhinosinusitis and bronchopneumonia. Interestingly, there was a case of facial paralysis. This fact supports the idea that viral infections may create a wide range of complications in children (19).

In conclusion, among the children with acute upper respiratory tract infection seen on an outpatient basis, the rate of virus isolation was 29.8%. The most commonly isolated viruses were influenza-A (36.6%), ADV (28.3%) and PIV (14.9%). RSV was especially common in infants under 6 months of age. While symptoms did not show any difference according to viral causes, fever was rare in RSV but prominent in influenza-A and ADV infections. The overall rate of complications was 4.4% and of hospitalization was 1.5%, especially in children under 2 years of age.

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