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Original Article

RSV infection in Istanbul: risk factors and frequency

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Abstract

Introduction: Respiratory syncytial virus (RSV) is one of the most common causes of acute respiratory infections in all age groups especially under two years. The aim of this study was to investigate the frequency and clinical features of RSV in hospitalized children under two years of age with the diagnosis of lower respiratory tract infections (LRTI) in our region.

Methodology: Between September 2011- May 2013, hospitalized children aged 0-2 years with the diagnosis of viral LRTI, in which nasopharengeal secretions were tested for the presence of the RSV antigen, were included in this prospective study.

Results: Among the total of 361 hospitalized children who were investigated for RSV antigen, 138 (38%) were female and 223 (62%) were male. The mean age of the group was 5,7±5,1 months (0-24 months). RSV antigen in nasopharyngeal secretions was positive in 68 (19%) of 361 patients. RSV infection was detected significantly higher in December and January ($p = 0.003$). RSV positivity was significantly higher in patients aged under 6 months ($p=0.01$), with shorter duration of breastfeeding ($p = 0.02$), low socioeconomic status ($p = 0.02$), and also born with spontaneous vaginal delivery ($p = 0.007$). In RSV(+) LRTI group, children were associated with severe disease than RSV (- LRTI group ($p = 0.014$).

Conclusions: Since there is lack of data investigating the frequency and the risk factors of RSV respiratory infections in our region, the present study is important for providing new data. Furthermore, this is the second study investigating the correlation between RSV positivity and meteorological conditions in Turkey.

Key words: RSV; LRTI; children; risk factor.

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Introduction

RSV is an enveloped, single-stranded RNA virus of the *Paramyxoviridae* family which has two major subtypes, designated as A and B. In most outbreaks both of these subtypes play a role simultaneously, however A subtypes is related with more severe diseases. RSV is known as the most common cause of lower respiratory tract infections (LRTI) in children under one year of age [1]. According to systematic review and meta-analysis of global LRTI burden , RSV causes over 30 million LTRI cases in children younger than five years old each year, and 3.4 million of these patients are associated with severe disease. Low respiratory tract infections are responsible for 53,250 to 199,000 children deaths. More than 90% of RSV infection associated deaths are predicted to be seen in lower-income countries in the world [2].

There is limited data investigating the incidence and clinical features of RSV in Turkey. Dereli *et al* [3]reported the first data of RSV frequency in children under 2 years with the diagnosis of brochiolitis in 1994. They found RSV bronchiolitis frequency equal to 29% in 65 children [3]. In another two different studies, the frequency of RSV with LRTI in children was found to be 29.5% and 20% in 2005 and 2010, respectively [4,5]. The latest data on RSV incidence was reported by Hacımustafaoglu *et al* [6], who investigated 671 hospitalized children with LRTI and found the RSV positivity in 254 (38%) children.

Since there is lack of the data on RSV frequency and risk factors from Turkey, the present study aimed to determine the frequency, possible risk factors and correlation between weather conditions and RSV positivity in hospitalized children with LRTI under two years of age in our region.

Methodology

This prospective study was performed in a tertiary hospital of Kartal Dr. Lütfi Kırdar Training and Research Hospital. A total of 361 hospitalized children under two years with LRTI were included in this study between September 2011- May 2013. Children in

neonatal intensive care unit (NICU) were excluded. Moreover, no RSV antigen was detected in the hospital in June, July and August. For this reason, data from these months were not included.

Parents were informed of the study and informed consent was obtained before inclusion of any cases. The study protocol was approved by the Ethics Committee of Kartal Dr.Lütfi Kırdar Training and Research Hospital.

All children under two years of age hospitalized with the diagnosis of viral LRTI (pneumonia ±bronchiolitis) in Pediatrics departments were investigated for RSV antigen in nasopharengeal secretions. Nasopharyngeal samples were obtained through nasopharyngeal swab standard method [7]. RSV antigen was determined in 20 minutes by immunochromatography using Abbott RSV Respi-Strip (Rapid Diagnostic Test for Syncytial Virus Detection in nasopharyngeal Specimens, Gembloux-Belgium). At the same visit, a questionnaire was administered to all parents for the risk factors of RSV infection. Date of hospitalization, education and economical status of parents, number of persons in the household, breastfeeding and cigarette smoke exposure were questioned. The day of discharge, length of hospital stay and clinical course of the disease were recorded. On the same day of RSV nasopharyngeal swabs collections, data on temperature, humidity and pressure regarding the climate was obtained from daily records of the General Directorate of Meteorology, Ministry of Forestry and Water Affairs.

After the detailed physical examinations, O_2 saturation with pulse oximeter, total blood count, C-reactive Protein level and posteroanterior (PA) radiograph of the lungs were performed in all children.

Table 1. Demographic characteristics and risk factors of children with RSV-positive and RSV-negative LRTI.

Variables		RSV (-) (n:293)		RSV (+) (n:68)		p value
		n	%	n	%	
	Male	180	61	43	63	
	Female	113	39	25	37	
		6.2 ± 5.4		3.8 ± 3.1		
		n	%	n	%	
	0-1 months	18	6	8	12	
	> 1-6 months	171	58	48	71	
	> 6-12 months	67	23	11	16	
	> 12-24 months	37	13	1	1	
	Preterm	40	14	7	10	
	Term	253	86	61	90	
	Spontaneous vaginal	128	44	42	62	
	Cesarean section	165	56	26	38	
	0	92	31	20	29	
	1	103	35	25	37	
	2	64	22	14	21	
	≥ 3	34	12	9	13	
	Low	92	31	33	49	
	Middle	183	62	32	47	
	High	18	6	3	4	
	Yes	177	60	47	69	
	No	116	40	21	31	
	Yes	89	30	16	24	
	No	204	70	52	76	
	Yes	291	99	68	100	
	No	2	0,6	0	0,00	
	No education	32	11	7	10	
	Primary education	189	64	43	63	
	High school and university	72	25	18	27	
	No education	8	3	2	3	
	Primary education	182	62	40	59	
	High school and university	103	35	26	38	
Duration of breastfeeding (months)		4.6 ± 4.2		3.2 ± 2.6		**0.022**

LRTI: Lower Respiratory Tract Infection, RSV: Respiratory syncytial virus.

The normal level of C-reactive Protein based on the method used at our hospital was below 4 mg/dL.

Statistical analysis

Stastistical calculations were performed with NCSS (Number Cruncher Statistical System), 2007 for Windows (NCSS Corporation, Kaysville, USA). Besides descriptive statistical calculations (mean and Standard deviation and frequency), Pearson chi-square test, Fischer's exact tests were used for evaluation of qualitative data. Statistical significancy was set at $p < 0.05$.

Results

Among the total of 361 hospitalized children investigated for RSV antigen, 138 (38%) were female and 223 (62%) were male and the male/female ratio was 1.6. The mean age (months±standart deviation) of this group was 5,7±5,1 months (range 0-24 months). The mean age were 3,83±3,17 months and 6,2±5,44 months for RSV(+) LRTI and RSV(-) LRTI group, respectively ($p = 0.002$). RSV antigen in nasopharengeal secretions was founded to be positive in 68 (19 %), and negative in 293 (81%) of 361 patients. Patients were classified due to age as follows: 0-1 months, >1-6 months, >6-12 months and >12-24 months. RSV positivity was significantly higher in patients: aged under 6 months ($p = 0.01$), shorter duration of breastfeeding ($p = 0.02$), low socioeconomic status ($p = 0.02$), and also born with spontaneous vaginal delivery ($p = 0.007$). There was no difference in gender, number of siblings, history of prematurity, maternal age, cigarette smoke exposure, family history of asthma, history of acute otitis media, education of the parents and length of hospital stay of the patients, between both groups. Demographic characteristics and risk factors of children with RSV positive and negative LRTI were shown in Table 1. Significant difference of laboratory findings, clinical presentations and course between the RSV(+) and RSV (-) LRTI were shown in Table 2. Clinical presentations in RSV (+) patients were: cough (96%), tacypnea (72%), subcostal retraction (49%), rhinorrhea (41%), dyspnea (25%), fever (18%), nasal flaring (7%) and wheezing (7%). Apnea and stridor were not observed in our patients with RSV (-) LRTI. Statistically no significant difference between RSV positive and negative patients could be demonstrated for clinical presentations such as fever, rhinorrhea, tacypnea, dyspnea, subcostal retraction, nasal flaring, stridor, wheezing and apnea.

RSV infection was detected significiantly higher in December and January ($p = 0.003$). In winter RSV positivity was significantly higher than in spring and autumn ($p = 0.001$). No RSV positivity was detected in June, July and August. RSV positivity according to year were 41% (28/68) in January, 26% (18/68) in February, 12 (8/68) in March, 3% (2/68) in April and 18 % (12/68) in December.

At the same day of the RSV test, the mean temperature, relative humidity and athmospheric pressure of the day were recorded, according to Ministry of Forestry and Water Affairs, General Directorate of Meteorology. It was documented that RSV positivity was significantly higher in low temperature ($p = 0.001$), high relative humidity ($p = 0.01$) and high athmospheric pressure ($p = 0.01$). Correlation between meteorological conditions and

Table 2. Significance difference of laboratory findings, clinical presentations and course between the RSV-positive and RSV-negative LRTI.

Variables		RSV (-) (n:293)		RSV (+) (n:68)		p value
Leukocyte count (/mm^3)		12169 ± 5435		10095 ± 4017		**0.003**
Total duration of bronchodilatator treatment (day)		7.5 ± 3.8		6.3 ± 2.8		**0.016**
Attack number of bronchiolitis		1.6 ± 2.1		1.2 ± 1.1		**0.043**
Length of hospital stay		8,22 ± 3,68		7,76 ± 3,78		0,366
		n	**%**	**n**	**%**	
	Negative	140	48	42	62	
	Positive	153	52	26	38	
	Normal	56	19	3	4	
	Infiltration	197	67	50	74	
	Hyperaeration	40	14	15	22	
	No	45	15	3	4	
	Yes	248	85	65	96	
	No	270	92	55	81	
	Nasal CPAP	13	4	10	15	
	Intubation	10	3	3	4	
	Mild	259	88	51	75	
	Severe	34	12	17	25	

CRP: C-reactive protein, PA: Posterior-anterior, CPAP: Continuous positive airway pressure therapy, RSV: Respiratory syncytial virus.

Table 3. Correlation between weather conditions and RSV positivity.

		RSV (-) (n:293)		RSV (+) (n:68)		p value
Atmospheric pressure average (hPa)		1015.21 ± 7.59		1017.75 ± 8.96		**0.017**
Temperature (°C)		9.99 ± 5.8		7.25 ± 5.06		**0.001**
		66.89 ± 15.39		71.75 ± 14.17		
		N	**%**	**n**	**%**	
	≥ 1015 hPa	172	58.7	40	58.8	
	≤ 1014hPa	121	41.3	28	41.1	
	> 10 ℃	136	46.4	19	27.9	
	< 10 ℃	157	53.5	49	72.0	
Humidity	> %60	171	58.3	48	70.5	0.063

RSV: Respiratory syncytial virus.

RSV infection was shown in Table 3. No mortality was observed during the study.

Discussion

RSV is one of the most common causes of acute respiratory infections in early childhood. RSV infected children mostly have the clinical symptoms of upper respiratory infections, however 20%-30% of these patients develop LRTI with the first infection. In addition, it is reported that almost 1% to 3% of all children under 1 year of age will be hospitalized due to RSV- LRTI [8]. According to Center for Disease Control and Prevention Center (CDC) data, every year RSV causes 57,527 hospitalizations and 2.1 million outpatient visits among children under 5 years of age [9]. In Europe, RSV is responsible for 42% to 45% of hospitalizations in children younger than two years with LRTI due to RSV [10]. In their study which aimed to estimate global burden of RSV disease Nair *et al* [2] showed that 99% RSV-associated deaths occured in developing countries. All these studies show that RSV is still problematic especially in the developing countries. In Turkey, there is limited data about risk factors and RSV frequency especially in our region. Around 1990s in two different studies conducted in our country, RSV frequency was found to be 29% and 36% in children under five years of age, respectively [3,11]. After 2000s in the studies by Kanra *et al* [4], Hacımustafaoglu *et al* [6], and Hatipoglu *et al* [12], RSV frequency were found to be 29.5%, 37.9% and 35% in children, respectively. *Kanra et a l*[4] conducted a multicenter prospective study between 2000-2002, in which 64% of the patients were born before 35 weeks of gestation; it also repotred that 11% had bronchopulmonary dysplasia (BPD), 20.8% had congestive heart failure and 3% had immunodeficiency. The study of Hatipoglu *et al* [12] was done in Istanbul between January-April 2006, among 80 hospitalized children with LRTI (28 patients with RSV positivity) under 2 years of age. Hacımustafaoglu *et al* [6], studied children with LTRI < 2 years old in three different hospitals in Bursa between March 2010 and February 2011. In our study, RSV positivity was found to be 19%. In southern areas of Turkey, different RSV positivity results were found. Çelik *et al* [13] studied children with LTRI aged 2-24 months in Mersin between July 2008-June 2010 and found a 5.2%.RSV positivity. On the other hand, Sağlık *et al* found a 26.5% RSV frequency in children under 5 years with LTRI diagnosis in Antalya [14]. However, a previous study in our hospital conducted between September 2009-April 2011 with the same methodology, showed that RSV positivity was 35% in children < 2 years who were hospitalized for LRTI [15]. In this study, we found RSV positivity in lower rate. There have been no studies during the same years in our region. For this reason we could not compare our results with any other study. In our opinion, one of the reasons for this finding was not having included the patients hospitalized in our neonatal intensive care unit. Also the patients in our study had no underlying chronic disease such as bronchopulmonary dysplasia (BPD), chronic pulmonary diseases, immunodeficiency, etc. Moreover, our study was performed later than other studies and all of the premature children discharged from our neonatal intensive care unit had been under RSV prophylaxis with palivizumab according to the policy of our Ministry of Health and were under close control during RSV season.

In literature, common risk factors that increase LRTI with RSV in children are: being younger than six months of age, prematurity, underlying lung disease, congenital hearth disease, down syndrome, exposed to secondhand smoke, immunodeficiency status and infants who are born during the first half of the RSV season [16-20]. Risk factors of RSV positive LRTI are not well defined in our country. In our study, we found risk factors for RSV positivity such as: to be younger than six months, having a low socioeconomic status, shorter duration of breastfeeding and spontaneous

vaginal delivery. Alvarez *et al* [21], assesed the risk factors for RSV bronchiolitis by data synthesis of 60 relevant studies. They found low socioeconomic status and lack of breastfeeding as risk factors which are similar to our study. We found only few studies that investigate the method of delivery as a risk factor for RSV bronchiolitis. In 2014, Hendaus *et al* [22] reported that children delivered by cesarean section were at higher risk for RSV bronchiolitis than normal spontaneous vaginal delivery, however the difference was not significant. In another study, cesarean section delivery was found to be a significant risk factor for RSV bronchiolitis [23]. As far as we know, our study is the first one to describe vaginal spontaneous delivery as a risk factor for RSV bronchiolitis. There might be some real factors behind this, for this reason we are not sure that this can be considered a real risk factor. Because of lack of data, the method of delivery is not well-defined as a risk factor for RSV LRTI, so further studies are needed. Kanra *et al* [4] conducted one of the largest study that investigated the risk factors for RSV in children with respiratory infection in our country. They reported that otitis media was more common in RSV positive patient than RSV negative patients. However, they found no difference in gender, age, age of gestation, family education, number of siblings, cigarette smoke exposure, underlying disease and length of hospital stay between the two groups. Similar to that study, we also found no difference in gender, number of siblings, prematurity history, education of the parents and length of hospital stay of the patients from both groups. Furthermore, there was no difference in maternal age, family history of asthma and acute otitis media between the two groups in our study. We have recorded all the clinical symptoms of the patients with RSV positive and negative LRTI. Although, there was no difference in fever, rhinorrhea, tacypnea, dyspnea, subcostal retraction, nasal flaring, stridor, wheezing and apnea as symptoms between the two groups, cough was much more common in RSV positive patients. Hatipoglu *et al* [12] reported that, rhinorrhea and fever were more common in RSV positive patients however, similar to our study, they found no difference in retraction, apnea, dsypnea, acute otitis media and wheezing between two groups. They compared CRP positivity between RSV positive and RSV negative patients and similar to our study, they found that C-reactive protein positivity was more common in RSV positive patients [12]. RSV induces seasonal outbreaks. In our study, RSV positivity was higher in winter time than other months similar to the study of Kanra *et al* [4] and Hacımustafaoğlu *et al* [6].

As far as we know, this is the second study that investigated the correlation between meteorological conditions and RSV positivity in children in our country. We found that RSV positivity was significantly higher in low temperature and high humidity similar to that study [24]. Additionally, we also reported that the atmospheric pressure and RSV positivity was found in higher rates. Hervas *et al* [25] explained in their study that this correlation is due to the fact that viral activity increases with atmospheric pressure.

Conclusions

In the present study, a 9% RSV positivity in hospitalized children under two years of age with the LRTI diagnosis was found. RSV positivity was significantly higher in patients, aged under 6 months, with shorter duration of breastfeeding, low socioeconomic status, and also born with spontaneous vaginal delivery. In the RSV(+) LRTI group, children were associated with severe disease more than the RSV (-) LRTI group. RSV is an important cause of LRTI. Many risk factors have been described in other studies, however, data about frequency and risk factors about RSV respiratory infection in our region of Turkey are limited. We performed one of the largest study investigating the risk factors, clinical features and correlation between meteorological conditions for RSV infection in Turkey, which can give hints for further studies. Because of the frequency and the severity of this illness, we believe that the best way to avoid this critical infection is a vaccine for RSV which has not been developed yet.

Authors' Contributions

EİG and YA analysed the data and drafted the manuscript, YA critically reviewed the analyses, EİG, YA, ERV, AAA, AK and FKN reviewed and commented on initial and final drafts of the manuscript, all authors read and approved the final manuscript.All authors have participated in drafting of the manuscript and/or critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

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