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Original Article

Clinical and virological characteristics of neonates admitted with acute lower respiratory tract infections

Akut Alt Solunum Yolu Enfeksiyonu Nedeni ile Yatırılarak İzlenen Yenidoğanların Klinik ve Virolojik Özellikleri

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Abstract

Aim: Viruses including respiratory syncytial virus, parainfluenza virus, rhinovirus are the primary etiologic agents in acute lower tract infections in neonates. We aimed to evaluate the clinical and demographic characteristics of newborns with acute lower tract infections.

Material and Method: Data was recorded from patients' medical records admitted between January 2013 and April 2016.

Results: The study population consisted of 43 neonates (19 girls, 24 boys). Mean gestational age and birthweight were 32 ± 4.4 weeks and 1735 ± 820 g, respectively. On admission, mean postnatal day and postmenstrual ages were 61 ± 48 days and 41 ± 4.3 weeks. Respiratory syncytial virus (n:8), rhinovirus (n:3), parainfluenza-3 virus (n:3) and adenovirus (n:3), respiratory syncytial virus and parechovirus (n:1), respiratory syncytial virus and adenovirus (n:1), rhinovirus and human bocavirus (n:1) were detected by polymerase chain reaction 20 patients in total. Siblings in the house (n:31), viral infection in the family (n:23), insufficient breastfeeding (n:15), bronchopulmonary dysplasia (n:13), siblings attending school (n:10) and being twin or triplet (n:7) were leading risk factors. Median hospital stay was 9 (1-60) days. Prematurity, fever, rales, respiratory support and feeding difficulty were statistically more common in polymerase chain reaction positive patients. Patients with the respiratory syncytial virus had higher gestational age, birth weight, less respiratory distress syndrome, surfactant use and patent ductus arteriosus, and lower postnatal day on admission than patients with other viruses ($p<0.05$).

Conclusion: Respiratory syncytial virus is the commonest cause of acute lower tract infections in newborns, but the clinical importance of co-infection and rare agents such as human bocavirus and parechovirus should be kept in mind. Supportive management is the mainstay of the therapy.

Key words: Neonates; viral pneumoniae; respiratory syncytial virus; polymerase chain reaction

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Öz

Amaç: Respiratuvar sinsityal virüs, parainfluenza virüs ve rhinovirüs yenidoğan döneminde akut alt solunum yolu enfeksiyonlarının en sık nedenidirler. Bu çalışmada alt solunum yolu enfeksiyonu mevcut olan yenidoğanların klinik ve demografik özelliklerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Yenidoğan yoğunbakım ünitemize Ocak 2013 ve Nisan 2016 tarihleri arasında yatırılan hastaların medikal kayıtları retrospektif olarak incelendi.

Bulgular: Çalışmaya 19'u kız 24'ü erkek olmak üzere 43 hasta alındı. Ortalama gestasyonel hafta ve doğum ağırlığı 32 ± 4.4 hafta ve 1735 ± 820 gr'dı. Başvuru anında ortalama postnatal gün ve postmenstrüel hafta 61 ± 48 gün ve 41 ± 4.3 haftaydı. Polimeraz zincir reaksiyonu testi sonucunda respiratuvar sinsityal virüs (n:8), rhinovirüs (n:3), parainfluenza-3 virüs (n:3) ve adenovirus (n:3), respiratuvar sinsityal virüs ve parechovirus (n:1), respiratuvar sinsityal virüs ve adenovirüs (n:1), rhinovirus ve insan bocavirüs (n:1) tespit edildi (toplam 20 hasta). Evde kardeş (n:31), ailede viral enfeksiyon (n:23), yetersiz anne sütü (n:15), bronkopulmoner displazi (n:13), okula giden kardeş (n:10) ve ikiz veya üçüz olma (n:7) en sık ana risk faktörleriydi. Ortanca hastanede kalış süresi 9 (1-60) gündü. Prematürite, ral, solunum desteği ihtiyacı ve beslenme güçlüğü polimeraz zincir reaksiyonu pozitif hastalarda istatistiksel olarak daha sıktı. Respiratuvar sinsityal virüs pozitif hastalar diğer virüslerin saptandığı gruba göre daha büyük gestasyonel hafta ve doğum ağırlığına sahipken daha az respiratuvar distres sendromu, surfaktan kullanımı, patent duktus arteriozus öyküsü mevcuttu ve semptomların başlangıcı ile hastaneye başvuru zamanı arasında geçen süre daha kısaydı.

Sonuç: Respiratuvar sinsityal virüs yenidoğanlarda alt solunum yolu enfeksiyonunun en sık rastlanan etkeni iken ko-enfeksiyon ve daha nadir görülen insan bocavirüs ve parechovirus gibi etkenlerin klinik önemi akılda tutulmalıdır. Destek tedavisi tedavinin en önemli bileşenidir.

Anahtar sözcükler: Yenidoğan dönemi; viral pnömoni; respiratuvar sinsityal virüs; polimeraz zincir reaksiyonu

1. Introduction

Acute lower respiratory tract infections (ALRI) is a fundamental cause of neonatal morbidity and mortality, especially in developing countries (1, 2). Viruses such as respiratory syncytial virus (RSV), parainfluenza virus (PIV), rhinovirus, human metapneumovirus (hMPV) are the major causes of ALRI in newborns (3, 4). Prematurity, low birth weight, bronchopulmonary dysplasia (BPD) and chronic aspiration are major clinical risk factors. Crowded daily life, having siblings, day-care attendance, smoke exposure are the demographic risk factors. Fever, cough, rhinorrhea, tachypnea, apnea, temperature instability, feeding difficulty and cyanosis are the main complaints. Studies mainly focused on RSV, which is the most critical pathogen in infants' first year of life (5, 6).

In this study, we aimed to evaluate newborns' clinical and demographic characters with ALRI and determine the distribution of pathogens.

2. Material and Method

This retrospective study took place in the neonatal intensive care unit (NICU) of Etlik Zubeyde Hanım Women's Health Care, Training and Research Hospital, University of Health Sciences Turkey, between January 2013 and April 2016. The local ethical committee of our hospital approved the study (27.06.2016/209). Clinical and demographic data were recorded from patients' medical records. ALRI was defined as the presence of fever, respiratory secretions, tachypnea, dyspnea and rales. Gestational age as weeks (w) (GA), birth weight, gender, mode of delivery, respiratory distress syndrome (RDS), surfactant delivery, BPD, palivizumab prophylaxis, smoking, crowding, history of respiratory tract infection in the family were recorded. Bronchopulmonary dysplasia was diagnosed based on the National Institutes of Child Health and Development diagnostic criteria (7). Insufficient breastfeeding was described as %50 of daily intake. Clinical and laboratory data also included chronologic age, oxygen or mechanical ventilation, laboratory evaluation results such as complete blood count, C-reactive protein, blood culture, chest x-ray, duration of hospital stay, complications, and mortality. Nasal swab samples were obtained for real-time multiplex polymerase chain reaction (PCR). Polymerase chain reaction study included RSV, coronavirus 43-63-229-HKU1, hMPV, parainfluenza-1-2-3-4, rhinovirus, adenovirus, enterovirus, parechovirus, H1N1, influenza A, B, human bocavirus (hBV) and performed by Public Health General

Directorship Laboratories, Ministry of Health. Patients grouped according to PCR results as positive and negative; and also as RSV and RSV coinfection, other viruses and negative groups to compare clinical and demographic characteristics.

Statistical Analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences, Version 20 for MAC. Clinical characteristics and laboratory variables were compared using the Student t-test, the Mann-Whitney U test, the ki square test. P<0.05 was considered to be statistically significant.

3. Results

The study population consisted of 43 neonates, including 19 girls and 24 boys. Mean GA and birthweight were 32 ± 4.4 w and 1735 ± 820 g, respectively. On admission, mean postnatal day (d) and postmenstrual age (PMA) were 61 ± 48 d and 41 ± 4.3 w, respectively. Age at the admission of preterm and term infants were 72 and 11 days, respectively (p<0.05). Thirty-four (79%) of patients were premature (<37 w), whereas 22 (51%) of patients' GA were ≤32 w. Nineteen patients (44%) were born by vaginal delivery. The polymerase chain reaction was performed in 33 patients.

Respiratory syncytial virus (n:8), rhinovirus (n:3), parainfluenza-3 virus (n:3) and adenovirus (n:3), RSV and parechovirus (n:1), RSV and adenovirus (n:1), rhinovirus and hBV (n:1) were detected **(Table 1)**. In 13 patients, PCR was negative. Risk factors were siblings in house (n:31), viral infection in family (n:23), insufficient breastfeeding (n:15), BPD (n:13), siblings attending school (n:10), being twin or triplet (n:7), tobacco smoke exposure (n:2) and chronic aspiration (n:2). Six patients were on palivizumab prophylaxis. The polymerase chain reaction was performed in 5 of these patients and resulted in rhinovirus (n:2) and negative (n:3). The most seen admission complaint was cough (58.1%), and others were fever (32.6%), respiratory distress (27.9%), nasal discharge (20.9%), cyanosis (18.6%) and grunting (14%).

Table 1. Polymerase chain reaction results of patients

Viral agents	n
Respiratory syncytial virus	8
Rhinovirus	3
Parainfluenza-3	3
Adenovirus	3
Respiratory syncytial virus + parechovirus	1
Respiratory syncytial virus + adenovirus	1
Rhinovirus + human bocavirus	1
Negative	13
Total	33

Physical examination findings were tachypnea (55.8%), retraction (60.5%), rales (46.5%), rhonchi (4.7%), hepatomegaly (7%), cyanosis (37.2%) and nasal secretions (16.3%). Apnea was seen in 4 patients (2 with parainfluenza-3 and 1 with adenovirus). The feeding difficulty was found in 12 (27.9%) patients. Empirical antibiotic treatment was given to 10 patients. There was no blood culture positivity and secondary bacterial pneumonia diagnosis in our study. Supportive treatment was the major treatment protocol in our study. X-ray abnormalities such as infiltration, reticular parenchyma or hyperaeration were found in 23 (53.5%) patients.

Seventeen patients needed oxygen support. Invasive and non-invasive mechanical ventilation support was given to 4 and 11 patients, respectively. Median duration of oxygen, invasive and non-invasive mechanical ventilation support were 6 (1-27), 2 (1-7) and 2.5 (1-13) d, respectively. Median hospital stay was 9 (1-60) d.

The polymerase chain reaction positive (n:20) and negative (n:13) patients had similar GA, birth weight, postnatal day, PMA, white blood cell count (WBC), C-reactive protein level, blood gas analysis results and hospital stay (p >0.05); but prematurity, fever, rales, need of respiratory support and feeding difficulty were statistically more common in PCR positive patients (p<0.05). Patients with other viruses had statistically lower GA, birth weight, more RDS, surfactant use and PDA; and higher postnatal day on admission but not PMA than patients with RSV and RSV con-infection (p<0.05) **(Table 2 and 3)**.

Patients ≤32 w GA (n:22) had statistically more cyanosis (p:0.04), lower median hemoglobin (9.6 vs 13.3 g/dl, p: <0.0<) and WBC (8040 vs 13,450/µl, p: 0.03); and longer duration of respiratory support (median, 11.7 vs 5.3 d, p: 0.04) and hospital stay (median, 18.3 vs 9.3 d, p: 0.04) than patients ≥33 w GA. The median postnatal day was higher in patients ≤32 w GA (86 vs 34 d, p: <0.0<), but PMA was similar (41.2 vs 40.5, p: 0.8) on admission. One patient died on treatment day 3. His GA and birth weight was 37 w and 2780 g. He admitted to the hospital on postnatal day 23, and his PCR was negative.

4. Discussion

Prematurity is the leading predisposing factor to ALRI. In our population, 34 (79%) of the patients were preterm infants, including 22 patients <32 w GA. Our prematurity rate seems to be higher than previously reported rates as 16.6-26.3% (6, 8, 9). This difference may be associated with our NICU's characteristics. It is well known that premature infants had a greater susceptibility to ALRI than term infants, especially in the first year of life (10). Most follow-up patients in our hospital are premature infants,

Table 2. Demographic characteristics of patients according to polymerase chain reaction results as respiratory syncytial virus and respiratory syncytial virus co-infection, other viruses and polymerase chain reaction negative groups

	PCR positive (n=20)		PCR negative (n=13)	p*	**
	RSV and RSV co-infection (n=10)	Other viruses (n=10)			
Gestational age (w, mean)	33.7 (±3.8)	29.8 (±2.5)	32.6 (±6.1)	0.6	0.02[a]
Birthweight (g, mean)	2110 (±850)	1375 (±580)	1945 (±1025)	0.6	0.03[a]
Age at diagnosis (w, median)	43 (13-90)	80 (21-149)	29 (3-181)	0.1	0.02[a]
PMA (w, median)	40 (36-42)	40 (34-50)	39 (36-50)	0.9	-
Male, n (%)	6 (60)	5 (50)	9 (69)	0.4	-
Cesarean section, n (%)	6 (60)	8 (80)	8 (61.5)	0.6	-
Breastfeeding (≥ %50), n(%)	9 (90)	5 (50)	8 (61.5)	0.7	-
Sibling at home, n(%)	9 (90)	8 (80)	8 (61.5)	0.2	-
Sibling attending school, n(%)	3 (30)	4 (40)	1 (7.7)	0.1	-
RTI at home, n (%)	7 (70)	7 (70)	5 (31.5)	0.07	-
Prematurity, n (%)	8 (80)	10 (100)	7 (53.8)	0.03	0.01[b]
BPD, n (%)	1 (10)	5 (50)	4 (30.8)	1	-
Tobacco exposure, n (%)	-	1 (10)	-	-	-
Chronic aspiration, n (%)	1 (10)	1 (10)	-	0.5	-
Palivizumab, n (%)	-	2 (20)	3 (23.1)	0.3	-

PCR: polymerase chain reaction; RSV: respiratory syncytial virus; PMA: postmenstrual age; RTI: respiratory tract infection; BPD: bronchopulmonary dysplasia
Data were presented as mean (±SD), median (min-max) and n (%)
* p value was calculated for PCR positive and negative patients
** only significant p values according to subgroup analysis were given
[a] Other viruses vs RSV and RSV co-infection
[b] Other viruses vs PCR negative

Table 3. Clinical symptoms of patients according to PCR results as RSV and RSV co-infection, other viruses and PCR negative groups

	PCR positive (n=20)		PCR negative (n=13)	p*
	RSV and RSV co-infection (n=10)	Other viruses (n=10)		
Cough, n (%)	8 (80)	6 (60)	5 (38.5)	0.7
Fever, n (%)	n (%)	1 (10)	7 (53.8)	0.04
Tachypnea, n (%)	7 (70)	4 (40)	7 (53.8)	0.9
Cyanosis, n (%)	4 (40)	7 (70)	5 (38.5)	0.3
Respiratory support, n (%)	9 (90)	10 (100)	7 (53.8)	0.01
CRP (mg/dl, median)	5 (0.01-17)	0.6 (0.01-6.2)	0.05 (0.01-2.8)	0.1
Duration of hospitalization (d, median)	8.5 (5-38)	9.5 (6-27)	7 (3-60)	0.4

PCR: polymerase chain reaction, RSV: respiratory syncytial virus, CRP: C-reactive protein
Data were presented as median (min-max) and n (%)
* p value was calculated for PCR positive and negative patients

leading to a high prematurity rate of admitted infants related to ALRI. The prematurity rate of patients with ALRI was reported as 11.2% and 29.2% by Garcia et al. and Alan et al., respectively (8, 11). Mean PMA was similar between preterm and term infants at admission. Preterm infants usually face respiratory viruses later than term infants because of NICU stay.

The respiratory syncytial virus was found to be the most common etiologic agent in our study, as in previous studies (12-14). Thirty per cent (n:10) of patients had RSV, including two patients (6%) with viral co-detection. Alan et al. reported that 19.6% of infants admitted to NICU for ALRI were diagnosed as RSV by monoclonal antibody test (11). In term infants, 33% and 42.6% of neonates with ALRI had RSV (4, 15). Aydin et al. used the rapid antigen test to diagnose RSV and found that 16.6% of infants were premature (6). Bilgin et al. reported that a causative viral agent was isolated in 119 of 243 infants, and 78% was RSV. Other viral agents were rhinovirus, coronavirus, parainfluenza, influenza A/B, metapneumovirus, enterovirus and adenovirus (16). In our study, 70% of patients were premature in the RSV group. In contrast to our study, Garcia-Garcia et al. reported that the most common viruses associated with pneumonia were adenovirus, rhinovirus, RSV and parainfluenza virus in early and moderate preterm infants (8). Rhinovirus, parainfluenza-3 and adenovirus were found to be the next most common etiologic agents in our study. Rhinovirus was reported to be the most second common virus in previous studies such as our study (4, 8, 14, 15). Viral co-detection was found in 3 (9%) neonates. Previous studies reported 7.1 to 29% viral co-detection rate (4, 8, 14, 17). We did not find any association between disease severity and viral co-detection, although previous studies reported both increased disease severity or no effect with viral co-detection (4, 18). We detected a parechovirus and rhinovirus co-detection. Parechovirus is usually responsible for sepsis-like illness and meningoencephalitis in neonates (19, 20). Emel et al. reported RSV co-detection with rhinovirus and coronavirus (17). Admission complaints and respiratory support they reported in their study were similar between RSV/RSV co-infection and other virus groups except for shorter hospitalization in other virus groups. Clinical symptoms of our patient may be attributed to rhinovirus. Human bocavirus was rarely reported as responsible for ALRI, but it should be noted that 10% of infants had bocavirus related upper respiratory tract infection (8). Interestingly, there was no influenza virus-related ALRI in our study. Previous studies did not report influenza positivity in patients with ALRI, while Bilgin et al. reported 3 ALRI cases related to influenza A/B (4, 8, 9, 16). This fact may be associated with an increased care of infants due to marked influenza symptoms in parents and awareness of the high contagion rate of influenza.

Risk factors for ALRI were prematurity, male gender, siblings in the house, viral infection in family, insufficient breastfeeding, BPD, siblings attending school, being twin or triplet, tobacco smoke exposure and chronic aspiration in our study as reported in previous reports (14, 21). Environmental risk factors such as siblings, viral infection at home were not different between groups. However, patients in the other viruses group were more premature than patients in RSV and RSV co-infection group; and had more morbidities related to prematurity such as RDS, PDA, BPD, and longer hospitalization days.

Fever, rales, respiratory support and feeding difficulty were more common in PCR positive patients as expected. Patients with RSV had more cough, fever, tachypnea, whereas other viruses group had more cyanosis. Previous studies reported a more severe clinical course of RSV infections than other viral infections (3, 4). Cough, retractions, crackles and rhonchi were found to be higher in the RSV group (n:93) than other viral infection groups (n:26), while postnatal age, haemoglobin and CRP were lower in the RSV group in a study from our country (16). They also found that apnea and RSV were risk factors for respiratory support. In contrast to previous studies need for respiratory support, duration of oxygen therapy and hospital stay, X-ray findings were similar between RSV and other virus groups in our study.

We think that the retrospective design of the study is a limitation. None of the patients had PCR evaluation. Family members with suspected respiratory tract infection could not be evaluated with PCR.

In conclusion, RSV is the commonest cause of ALRI in newborns, but the clinical importance of a co-infection and rare agents such as HBV and parechovirus should be kept in mind. Therefore, supportive management is the mainstay of the therapy, and antibiotics should be started for secondary bacterial infection.

Declaration of Interest

The authors report no conflict of interest.

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