Respiratory Syncytial Virus Bronchiolitis Iga LT-E4 Responses and Effects of Host Factors in Two Iraqi Pediatric Hospitals

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Abstract

Background : Respiratory syncytial virus (RSV) is a leading cause of lower respiratory tract disease in infants and young children.Both the magnitude, intensity of infection and the host response to RSV infection determine the severity and intensity of disease. Objective : Our goal was to evaluate the effect of immune response (RSV IgA) and inflammatory mediators (LT-E4), in addition to the influence of host factors on the severity of the disease. Methods : This was a randomized, prospective study in two Iraqi pediatric hospitals. Sixty infants (mean age: 6.99±0.62 ,35 boys 25 girls) ,with a first episode of acute bronchiolitis were randomly divided into four treatment groups: oxygen plus intravenous fluid, montelukast pediatric chewable tablet,salbutamol given in combination as oral plus nebulized salbutamol, and dexamethasone IV injection. Control infants with non respiratory diseases were also studied for comparisons. The measured parameters was RSV IgA titer, LT-E4 titer, and a variety of environmental and host factors that may contribute to the severity of RSV bronchiolitis.Severity of bronchiolitis was based on the quantization of lowest O2 saturation and the length of hospital stay. Results : There were significant increase in RSV IgA values in patients (1.58 ± 0.24 U/mL) compare to the control (0.36 ± 0,03 U/mL);also there were a significant increase in the leukotriene E 4 values in patients (2.66 ± 0.52 ng/ml) compared to the control infants(0.15 ± 0.007 ng/ml). Age was found to be a significant factor in the severity of infection. The younger an infant was, the more severe the infection tended to be as measured by the lowest oxygen (O2) saturation. We also found that infants exposed to postnatal cigarette smoke from the mother had a lower O2 saturation than those not exposed. Although a history of maternal atopy seemed to be protective. Conclusion : Secretory IgA antibodies level was found to be a good indicator to respiratory syncytial virus infection as seen by significantly higher levels in patients compared to the control infants. The severity of RSV bronchiolitis early in life seems modified by postnatal maternal cigarette smoke exposure, atopy and age of the infants.

Index terms— RSV, Respiratory Syncytial Virus IgA (RSVIgA); Leukotriene E-4(LT-E4), Bronchiolitis.

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Keywords : RSV, Respiratory Syncytial Virus IgA (RSV-IgA); Leukotriene E-4(LT-E4), Bronchiolitis.

espiratory syncytial virus (RSV) is the leading cause of serious respiratory tract infections in infants and young children throughout the world (1). RSV replicates for 1-3 days before producing lower respiratory tract symptoms affecting almost 60% of infants and up to 25% of toddlers and preschoolers. Current treatment approaches for severe RSV induced disease are ineffective. Therefore, prevention of disease is a high priority .Immunoglobulin

A(IgA) is the most abundant immunoglobulin in mammals. Unlike other antibody isotypes, IgA is targeted to mucosal tissues, and virus-specific IgA in mucosal secretions has been shown to protect from reinfection. IgA, unlike IgG, is able to bind and neutralize viral proteins intracellularly at the site of initial replication in epithelial cells .Therefore; mucosal IgA may be of particular importance in immunity against RSV, which is a mucosally restricted pathogen (2,3). Inflammatory mechanisms in bronchiolitis have been documented recently, including increased airway secretion, mucosal edema, and infiltration of inflammatory cells. Cysteinyl leukotrienes (CysLTs) are released during respiratory syncytial virus (RSV) airway infection in infants, and their levels are significantly elevated. CysLTs are known to cause bronchial obstruction, mucosal edema, and infiltration of eosinophilic granulocytes and to increase bronchial responsiveness (4). CysLTE4 (LTE4), one of the terminal CysLT metabolites, is significantly increased in the infants hospitalized with RSV bronchiolitis (5). The risk of severe RSV disease is increased by factors that compromise the ability to control and withstand a respiratory tract infection. Therefore; environmental factors also play a role, including ones that affect lung function (e.g., household tobacco use) or that increase exposure to infection (e.g., day care, hospitalization, multiple siblings, crowding) (6,7). The objective of the present randomized, prospective study was to evaluate the effects of immune response, inflammatory mediators, host and environmental factors on the severity of the acute viral bronchiolitis. This prospective study was conducted in two Iraqi pediatric hospitals. Baghdad Health Office/Karkh, Child's Central Teaching Hospital & Karbala Health Office, Karbala Pediatric Teaching Hospital. Inclusion criteria were infants' patients aged >8 weeks and <2 years with a respiratory symptom duration of<4 days. Additional inclusion criteria included first episode of wheezing or shortness of breath, randomization within 12 hours of admission and informed consent. Exclusion criteria were any previous hospital admissions with respiratory illnesses, had ever been treated with antiasthma medications before the current illness, corticosteroids treatment in any form during current illness, and underlying cardiopulmonary disease. Gender, age, weight, height , body temperature ,family history in (first-degree relatives), of asthma ,atopy, tobacco smoking, usage of kerosene heater ,type of feeding ,duration of exclusive breast feeding, concurrent diseases, and concomitant medications, were recorded for each infants .A total number of 60 patients mean age: 6.99±0.62 with mild to moderate bronchiolitis were divided randomly into four treatment groups:

Group A: Ten infants' patients had received oxygen + intravenous fluid. Group B: Ten infants' patients had received study treatment, montelukast pediatric chewable tablet 4mg once daily, if vomiting occurred one additional dose was given. Group C: Twenty infants' patients had received salbutamol given in combination as syrup & by nebulization, (oral salbutamol 0.1-0.3mg/kg/dose q8 hour+salbutamol nebulizer 0.01-0.02 mg/kg /dose q6hour). Group D: Twenty infants' patients had received dexamethasone ampoule (4mg/1ml), with a dose of, 0.25 -0.5 mg/kg/dose q 12 hours intravenously.

From all enrolled infants, blood samples were taken and try to measure both (RSV IgA) & LT-E4, antibody to RSV & inflammatory mediators that release during RSV acute bronchiolitis, respectively. These parameters were measured by the enzyme linked immunoassays (ELISA), to investigate the etiology of acute respiratory infections in hospitalized infants .The test was explained to the parents and they signed the informed consent form. The obtained optical density (OD) of the standards (y-axis, linear) are plotted against their concentration (x-axis, logarithmic) either on semilogarithmic graph paper or using an automated method (8,9,10) .

Other type of samples that taken from the patients that put on the study treatment, montelukast pediatric chewable 4mg tablets, was the nasal swab. In the present study, we prospectively tried to examine the association between the presence of nasal eosinophils and severity of acute bronchiolitis and the effect of montelukast on nasal eosinophil. In this study we tried to quantify the number of neutrophils and eosinophils in nasal secretions by utilizing the semiquantitative nasal cytology grading score by Meltzer (11,12) . The values of weight,& duration of exclusive were expressed as mean ± standard error of mean (SEM).

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The table (2) showed the RSV IgA values for infants' patients with acute viral bronchiolitis, together with RSV IgA values for the control infants. There was a significant increase in RSV IgA values in patients compared to the control infants. There was a significant relationsihips between titer of the antibody against RSV(RSV IgA) and family history of atopy,tobacco smoking ,and the ages of infants patients.

Table (1), demonstrated that, there were no significant differences between the groups in terms of demographic variables.

Table (2): Relationships between host factors and RSV IgA titer for infants' patients with acute viral bronchiolitis and for the control infants. Data were expressed as mean ± standard error of mean (SEM), number (n) and percent (%). Control :infants with non respiratory illness Table (3) showed the leukotriene E4 values in infants patients with acute bronchiolitis, together with leukotriene values of the control infants. There was a significant increase in the leukotriene E4 values in patients compared to the control infants As the table shown, only the gender and family history of tobacco smoke showed significant differences.

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Table (4) Effects of host factors on length of stay (LOS) and oxygen saturation (S P O2) for the infants patients with acute viral bronchiolitis .Data were expressed as mean ± standard error of mean (SEM) ,number (n) and percent (%).

Table (4) showed the effects of host factors on the length of hospital stay (LOS) and oxygen saturation (S P O 2) in infants patients with acute viral bronchiolitis. As the table shown, only the host factors of family history of atopy and breast feeding of infants showed significant effects on duration of hospital stay and oxygen saturation of blood.

Concerning nasal swab from infants' patients with acute viral bronchiolitis before and after treatment with montelukast chewable 4 mg tablets once daily; according to Meltzer grading there was a significant differences in the count of eosinophils -neutrophils before and after treatment with montelukast ; 1. 6 reinfection can readily occur throughout life without significant antigenic change .The relative contribution of viral versus various host factors to RSV pathogenesis remains controversial (6). The immune response to primary RSV infection is generally inefficient and consequently subsequent reinfections are common throughout life. In RSV infection, innate and adaptive immunity are out of balance (13).

Comparing the risk factors with RSV IgA values of infants' patients, only the age, history of atopy and passive tobacco smoking showed significant differences (14). In the age category older infants' patients (over 1 year) had significantly higher RSV IgA value compared to younger patients (below 1 year) . Patients with negative family history of atopy had significantly higher RSV IgA value compared to patients with positive history of atopy. On the other hand patients with positive history of passive tobacco smoking had significantly higher RSV IgA value compared with those of negative history of passive tobacco smoking. This could indicate that, parental smoking did not inhibit the production of antimicrobial IgA, suggesting that other factors are responsible for the increased susceptibility to infection in these infants. Infants who lived in tobacco smoking environments had increased severity of disease, as results of Th2 predominance, with decreased expression of Th1 cytokines (15) , and IgA titer was less effective for protecting against RSV infection (2) . Lanari et al. (**??**002) (14) , demonstrated that exposure to cigarette smoke, in general, seems to worsen the severity of the viral bronchiolitis.

Comparing the risk factors with LTE4 values, only the gender and family history of tobacco smoke showed significant difference. Concerning the gender, the value in female babies was significantly higher than male babies. This could indicate that the females infants had more sever RSV infections compared to male infants; this has been attributed to the tendency of parents to bring sick male babies to the hospital earlier than female babies (3) .CysLT increased in infants who exposed to the tobacco smoke. This could indicated that, the exposure to the tobacco smoke increases the severity of RSV bronchiolitis, which was described here by the increased level of LTE4 in the infants who lived in tobacco smoking environments (16,17,18).

Comparing the effects of host factors (age, sex, family history of asthma, atopy, tobacco smoking, kerosene heating, presence of pets at home, breast or bottle feeding and number of family members) on the length of hospital stay and oxygen saturation in infants with acute viral bronchiolitis; only the host factors of family history of atopy and breast feeding of infants showed a significant effects on duration of hospital stay and oxygen saturation of blood (19) . Infants with a positive family of atopy showed a shorter duration of hospital stay and a higher value of blood oxygen saturation compared to infants with acute viral bronchiolitis and have no family history of atopy. Breast feeding of infants with acute viral bronchiolitis showed a significant effect on the blood oxygen saturation and length of hospital stay. Breast feeding is protective, through either transfer of maternal antibody or enhancement of virus-specific lymphocyte transformation activity. Infants with breast feeding have a shorter length of stay and higher value of blood oxygen saturation relative to infants without having breast feeding and have bottle fed.

This finding is substantiated further by the fact that infants with a higher O2 saturation spent less time in the hospital than infants with a lower O2 saturation (14) .

Regarding to the effects of RSV IgA level on the length of hospital stay and patients oxygen saturation, there were a significant effects on both length of hospital stay and patient oxygen saturation. Infants with low titer of RSV IgA showed longer period of hospital stay & lower values of oxygen saturation compared to the patients with a high titer of RSV IgA , which could indicated effects of immune response of the patients on the resolution of symptoms and the time at which patients were fit to the discharge (7,20) . Regarding to the effects of inflammatory mediators' cysteinyl leukotriene and its metabolite LTE4 on the period of hospital stay and oxygen saturation of infants patients with acute viral bronchiolitis, there were significant effects. High titers of LTE4 associated with prolong hospital stay and lower value of blood oxygen saturation .Female, younger infants, negative family history of atopy, and absence of breast feeding, showed longer period of hospital admission & lower value of blood oxygen saturation.

According to Meltzer grading there were a significant differences in the counts of eosinophilsneutrophils before and after treatment with montelukast tablet for the infants patients with acute viral bronchiolitis. This could indicated that eosinophilrecruiting chemokines are strongly produced and released from bronchial epithelial cells after stimulation with RSV (12) ;and montelukast treatment has been shown to reduce eosinophils in nasal mucosa of infants (21) .

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The relationships between risk factors and RSV IgA titer in infants with viral bronchiolitis, only age, family history of atopy and tobacco smoking showed significant effects. Patients with low titer of RSV IgA showed longer period of hospital stay & lower values of oxygen saturation comparing to the patients with a high titer of RSV IgA. Concerning the relationships between risk factors of infants with bronchiolitis and leukotriene E4 level, only the gender and family history of tobacco smoke showed significant difference. There were a significant effects of high level of LTE4 on the period of hospital stay compared to the low level of LTE4.

Host factors of family history of atopy and breast feeding of infants showed significant effects on duration of hospital stay and oxygen saturation of blood. Infants exposed to postnatal cigarette smoke from the mother had a lower O 2 saturation than those not exposed. Infants with a family history of atopy especially a maternal history of asthma had a higher O 2 saturation. Infants with highest blood oxygen saturation, have shorter length of hospital stay.

There were significant differences in the count of eosinophils -neutrophils before and after treatment with montelukst,which could indicated that, there was a correlation between nasal eosinophil and severity of viral bronchiolitis .

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	Patients (n total =60)	Control Infants (n total =20)
Characteristics	(n,%)	(n,%)
Age <6months.	40, (59)	12, (60)
Age >6months.	20, (41)	8,(40)
Male.	35 ,(58)	14, (70)
Female.	25 ,(42)	6 ,(30)
Family history of asthma.	30, (52)	8 ,(40)
Family history of atopy.	38 ,(63)	12, (60)
History of passive tobacco smoking.	44,(74)	16, (80)
Family history of kerosene heating.	46 ,(77)	14, (70)
Presence of pets at house.	26, (45)	10, (50)
Breast feeding.	33 ,(54)	2, (10)
Bottle feeding.	18,(30)	14 ,(70)
Mixed feeding.	8,(13)	4, (20)
< 5 Member.	8,(13)	4,(20)
>5 Member.	52,(87)	16(80)
Mean weight, kg.	7.2 ± 0.79	9.3 ± 1.14
Duration of exclusive breast feeding, months.	4.53± 0.303	8 ± 2.68

Figure 1: Table (1

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	Patients		Pat
	n ,(%) n ,(%) total = 48	Patients	U/r Pat
LT-E4 High Titer.			2.66
LT-E4 Low Titer.		total = 45	0.14
RSV IgA high titer (mean ± SEM) RSV IgA low titer (mean ± SEM) Age <1year. Age >1 year.	36 (75) 12 (25)		1.58
Age <1year. Male.	34,(70.8)	34 (75.6)	1.24
Age >1 year. Female.	14,(29.1)	11 (24.4)	2.63
Male. Positive Family history of Asthma. Female. Negative Family history of Asthma. Positive Family history of Atopy.	23,(47.9) 25 (52.1) 34 (70.8)	34 (75.6) 11 (24.4)	1.37
Positive family history of asthma. Negative Family history of Atopy.	14 (29.1)	21,(46.6)	1.21
Negative family history of asthma. Positive History Of Passive Tobacco		24(53.3)	1.91
Positive family history of atopy. Smoking. Negative History Of Passive Tobacco	38 (79.2)	33 (73.3)	1.18
Negative family history of atopy. Smoking.	10(20.8)	12 (26.6)	2.69
Positive history of passive tobacco smoking. Positive Family history of Kerosene Heating.	40 (83.3)	35 (77.7)	1.79
Negative history of passive tobacco smoking. Negative Family history of Kerosene Heating.	8 (16.6)	10(22.2)	0.86
Positive family history of kerosene heating. Positive Presence of Animal in the house.	20(41.6)	38 (84.4)	1.49
Negative family history of kerosene heating. Negative Presence of Animal in the house.	28 (58.3)	7 (15.6)	2.21
Positive presence of animal in the house. Positive Breast Feeding.	29 (60.4)	20(44.4)	1.26
Negative Presence of animal in the house. Negative Breast Feeding. Positive breast feeding. Positive Bottle feeding. Negative breast feeding. Negative Bottle feeding. Number Of Family Member > 5.	19 (39.6) 20 (41.6) 28 (58.3) 36 ,(75)	25 (55.5) 22(48.8) 23 (51.1)	1.84
Positive bottle feeding. Number Of	12	21,(46.6)	1.41

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