

Respiratory Syncytial Virus Infection: IgA & LT-E4 Responses and Effects of Host Factors for Infants with Acute Bronchiolitis 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.

Index terms— Pediatric; RSV, Respiratory Syncytial Virus IgA (RSV-IgA); Leukotriene E-4(LT-E4), Bronchiolitis.; Cysteinyl Leukotrienes; Secondhand Cigarette Smoke;

1 Introduction

Respiratory 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 R control infants. The severity of RSV bronchiolitis early in life 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 123 patients mean age: 6.99 ± 0.62 with mild to moderate bronchiolitis were divided randomly into eight treatment groups:

Group A: Ten infants' patients had received oxygen + intravenous fluid. Group B: Fourteen infants' patients had received study treatment, montelukast pediatric chewable tablet 4mg once daily, if vomiting occurred one additional dose was given (4). Group C: Ten infants patient had received azithromycin suspension (200mg/5ml), with a dose of 10 mg /kg once daily. Group D: Ten infants' patients had received hydrocortisone vial (100 mg/2ml), with a dose of, 5-10 mg/kg/dose q 6hour IV. Group E: Twenty infants' patients had received salbutamol syrup (2mg/5ml), with a dose of, 0.1-0.3 mg/kg/dose q 8 hour; the method of syrup administration was taught to the caregiver. Any patient who vomited the drug within 15 minutes of ingestion was advised to have a repeat dose (8). Group F: 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 G: Twenty infants' patients had received dexamethasone ampule (4mg/1ml), with a dose of, 0.25 -0.5 mg/kg/dose q 12 hours intravenously. Group H: Nineteen infants' patients had received salubutamol solution for nebulizer (5mg/ml), with a dose of, 0.01-0.02 mg/kg /dose q 6 hour.

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 (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).

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4 Materials & Methods

Table ?? : Demographic data and baseline characters of patients and control infants. The data were expressed as number (n), and percentage (%).

Table (1), demonstrated that, there were no significant differences between the groups in terms of demographic variables. The values of weight, & duration of exclusive were expressed as mean \pm standard error of mean (SEM). III.

5 Results

Table ?? : 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 \pm standard error of mean (SEM), number (n) and percent (%).

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 relationships between titer of the antibody against RSV(RSV IgA) and family history of atopy, tobacco smoking, and the ages of infants patients. ??able 3 : Relationships between host factors and leukotriene -E4 for infants' patients with acute viral bronchiolitis and for the control infants. Data were expressed as mean \pm standard error of mean (SEM), number (n) and percent (%).

Table (3) showed the leukotriene E4 values in infants patients with acute bronchilitis, 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. ?? : 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 \pm 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 O2) 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 montelukst ; 1.6 ± 0.32 versus 0.33 ± 0.16 respectively. This could indicated eosinophil-recruiting chemokines were strongly produced and released from bronchial epithelial cells after in vivo stimulation with RSV.

RSV is a highly infectious and prevalent virus. More than other respiratory viruses, RSV infection can occur very early in life despite maternal antibodies, and 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. (2002) (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 effects 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 a 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 montelukst 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 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 IV.

6 Discussion

V.

7 Conclusion

titer of RSV IgA. Concerning the relationships between risk factors of infants with bronchitis 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 O₂ saturation than those not exposed. Infants with a family history of atopy especially a maternal history of asthma had a higher O₂ 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 montelukast, which could indicate that, there was a correlation between nasal eosinophil and severity of viral bronchiolitis.^{1 2}

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