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ORIGINAL ARTICLE

Serum Chitinase3-like Protein 1 (YKL-40) in Wheezy Infants.

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ABSTRACT

Background: Chitinase-3-Like Protein 1(YKL40) is an inflammatory biomarker secreted from neutrophils, epithelial cells and smooth muscle cells of airways. It has been expressed in diseases characterized by inflammation and tissue remolding of respiratory tract e.g., asthma. Little reports were described in wheezing infants. The aim of this study is to estimate serum YKL40 in wheezy infant and study its role in pathogenesis in different types of wheezes which may help in diagnosis and management of the disease.

Methods: The study was carried on 49 infants with wheezes ,23 has recurrent wheezes ,26 has no recurrent wheezes. Detailed medical history and examination were done. Laboratory investigations were done including Complete blood count (CBC) with differential counts, C-reactive protein (CRP), blood gases were done. Chest x-ray and C.T. scan were done when required for persistent wheezing, YKL-140 was assessed by enzyme linked immune assay kits.

Results: Serum YKL 40 did not show any relation to neonatal intensive care unit (NICU) admission or recurrence of wheezing. Cases with family history of asthma showed higher level compared with those without family history. Also, critical cases showed higher values compared with stable cases. However, cases without family history of wheezing and stable cases showed no difference in serum YKL 40 compared to control. No significant difference between cases and control regarding WBCs, RBCs, platelets and CRP, while cases showed lower Hb and higher, neutrophil, serum YKL40 compared with control. Serum YKL140 showed positive correlation with neutrophil counts.

Conclusion: Serum YKL140 was significantly higher in wheezing infants compared to control. Cases with family history of asthma showed higher level of this marker compared with those without family history of asthma. It showed positive correlation with blood neutrophil. These results have diagnostic and prognostic significance regarding infant wheezes.

Keywords: Serum Chitinase 3-like protien1 KYL-40, infant wheezes, atopic, recurrent, non-recurrent.

INTRODUCTION

Serum chitinase-3 like protien-1 "YKL-40" is an inflammatory biomarker associated with disease activity and mortality in patients with diseases characterized by inflammation and tissue remodeling [1]. The site of formation, action and relation to disease state of YKL-40 is subject of research in recent years [2]. It is secreted from cells in the airway mucosa, i.e., neutrophils, macrophages, and airway epithelial cells [3]. It is induced at sites of inflammation, infection, and tissue remodeling, suggesting that this protein plays active roles in anti-infective defense and repair responses [4].

In adults, increased serum YKL-40 has been associated with asthma, and its levels correlate with increasing disease severity and bronchial wall thickness as well as decreasing lung function [5].

In pediatrics, YKL-40 it was studied in different pulmonary diseases for monitoring and diagnosis. YKL-40 in bronco-alveolar lavage is reflective of inflammation in early cystic fibrosis lung disease in children [6]. Significant association between

serum chitinase-3-like protein-1 (YKL-40) and lung function in children with asthmatic symptoms was detected.

This association was focused on indices that reflect small airway function [7]. It was found to be higher in children with pneumonia and has prognostic value in those with viral pneumonia [8].

Wheezing is a common challenge in early childhood. About 50 % of children experienced one wheezing episode in 1st 6 ys. One third had one episode of wheezing in the preceding 6 winter months [9]. There are 3 phenotypes of wheezes: 1-Early transient wheeze (20%) start before 3years and ends before 6 ys 2-Late onset (15%) starts between 3-6 ys , and 3-Persistent wheezes (14%) starts before 3 ys and continue after 6 years and divided into 2 types atopic or IgE mediated and non-atopic type [10].

Little reports available about serum YKL 40 in infant wheezes. In preschool children YKL 40 was significantly higher in wheezing infant compared to control but not related to persistent wheezing [11]. It was higher in post infectious bronchiolitis obliterans exacerbation compared to acute bronchiolitis [12].

For further information about its role of in pathogenesis and management in respiratory diseases in children we measured YKL-40 in wheezy infants. Also, we hope to study its role in different types of wheezes.

METHODS

Patients group: Forty-nine patients who suffered from wheezing were included in this study. 23 were suffered from recurrent wheezes while 26 has no recurrent wheezing.

Detailed medical history including admission in NICU, chest diseases, allergies and smokes exposure. Family history of asthma, atopic and immunological diseases were taken. Complete physical examination and growth assessment were done including weight, height. Cases were classified according to clinical presentation into two groups :-1-stable cases those cases presented with feeding amount less than usual but still > half of normal amount , signs of breathing difficulty , respiratory rate (R.R.) <60/min , no grunting , moderate retraction , wheezing, O2 saturation 88-92% and generally look irritable 2-ceitical(severe cases), those cases presented as moderate cases + grunting , severe retraction , O2 saturation <88% , feeding decreased to less than half amount , generally look lethargic [13] Laboratory investigation included CBC with differential count, CRP. Blood gases was assessed. Chest x-ray and C.T. scan were done when required for persistent wheezing, YKL-40 was assessed by enzyme linked immune assay kits.

Sample Collection: Blood samples were obtained by venipuncture from each subject and divided in two tubes. 1st tube with K2EDTA for blood count and blood film 2nd tube is allowed to coagulate for 30 minutes at room temperature. Serum was separated by centrifugation for 10 min at 3000 rpm and stored at -70 till tests were done.

Quantitation of human chitinase-3 like-proten-1(YKL40): Human serum chitinase-3-like protein 1 (YKL40) was analyzed according to manufacturer instruction by ELISA using human YKL40 kit (Cat No E2063Hu) supplied by Bioassay Technology Laboratory (China).

Principle of the assay: The kit is enzyme linked immunosorbent assay. The plate has been pre-coated with human (YKL40) antibody. YKL40 present in the sample was added and bind to antibodies coated on the wells and then biotinylated human YKL40 antibody was added and bound to YKL40 in the sample. Then streptavidin- horseradish peroxidase (HRP) was added and bound to biotinylated YKL40 Ab. After incubation unbound streptavidin-HRP was washed away. Substrate solution was then added and color developed in proportion to the amount of YKL40. The reaction is terminated by addition of acidic stop solution and absorbance is measured at 450 nm.

Inclusion criteria infants with wheezes with age ranges from 1-24 months whether recurrent or non-recurrent, those who are stable (moderate respiratory distress) or critical (has severe distress).

Exclusion criteria: Cases with congenital lung lesions, suspected immune deficiency gastro-esophageal reflux disease "GERD", possible cardiac, mediastinal lesion was included in the study.

Control group: Fifteen children age and sex matched were selected as control group. These cases were taken from OPD clinic came for routine check or minor illnesses.

STATISTICAL METHODS

Data were analyzed using SPSS 20 computer program (IBM, Endicott, Broome County, New York, United States). Data were expressed as mean ± SD for categorized variables. Tests of significance "Chi-square and T tests" and correlation study were done when appropriate. The correlation coefficient method was used to correlate different parameters. P value > 0.05 = statistically insignificant, P ≤ 0.05* = statistically significant, P < 0.01**= highly significant.

RESULTS

Forty-nine (49) infants suffered from wheezing were included in this study. 23 had recurrent wheezing while 26 had 1st attack of wheezing ,24 has positive (+ve) family history of asthma while

25 cases had negative(–ve) family history, 21 had had NICU admission while 28 had no history of NICU admission (Table 1).

Our cases were age, weight and sex matched with control cases (P was 0.446,0.564 and 0.567 respectively) (Table 2).

Serum YKL-40 did not show any relation to NICU admission, recurrence or severity of wheezing, (P was 0.612, 0.334 and 0.513 respectively). Cases with family history of asthma showed higher level compared with those without family history (P was 0.003) (Table 3). However, cases without family history of wheezing showed no difference in serum YKL 140 compared to control (P was 0.562).

No significant difference between cases and control regarding WBCs, RBCs, platelets and CRP (P was,0.727, 0.224,0.479 and 0.323 respectively), while cases showed lower Hb and higher, neutrophil, serum YKL40 (P was 0.031 ,0.027 and 0.028 respectively) compared with control (Table 4).

Serum YKL 140 did not show any correlation with age, weight, WBCs , RBCs ,platelets ,CRP or Hb (P was 0.927, 0.429 ,0.842 ,936 ,0.541 ,and 0.27 respectively) while showed positive correlation with neutrophil count (P was 0.009) (table 5) (Figure 1).

Table 1: Cases regarding clinical presentation

Symptoms		Number of cases	percentage
Wheezing	Recurrent	23	46.9%
	Non-recurrent	26	53.1%
Family history of asthma	+ve	24	49%
	-ve	25	51%
NICU admission	+ve	21	42.9%
	-ve	28	58.1%
Severity of wheezing	Stable	34	69.4%
	Critical	15	30.6%

NICU: Neonatal Intensive Care Unit

Table 2: Demographic data for cases and control

	Cases (49)	Control (15)	P
Age (months) "MW"	2-24(12)	2-24(12)	0.446
Weight "T-test"	9.19±2.5	9.5±1.8	0.564
Sex (chi square) M F	22 27	8 7	0.576

MW: Man-Whitney

Table 3: Serum YKL40 relation to clinical data using Man-Whitney Test

Wheezing recurrence	Recurrent (23)	10-50(19)	P:0.334
	Non-recurrent (26)	10-55(17.5)	
Family history of asthma (FHA)	+ve(24)	12-55(26)	P: 0.003
	-ve(25)	12-50(15)	
NICU admission	+ve(21)	10-50(16)	P: 0.612
	-ve(28)	10-55(18)	
Severity of wheezing	Critical (34)	10-55(20)	P:0.513
	Stable (15)	10-50(17.5)	

YKL-40: Serum Chitinase3-like protein1**, NICU:** Neonatal Intensive Care Unit

Table 4: Laboratory data in wheezy infant versus control

		Patients (49)	Control (15)	p
CRP (mg)"MW"		1-38(12)	12-24(12)	0.323
WBCs ($\times 10^3$) "MW"		3-20(8.7)	6-13	0.727
Neutrophil ($\times 10^3$) "MW"		1.5-6(3)	2.3-3(2.7)	0.027
RBCs (10^6) T-test		4.2±0.684	4.43±0.39	0.224
Hb(gm) T-test		11.73±1.27	12.18±1.13	0.031
Platlets$\times 10^3$ T-test		110-620(350)	250-580(350)	0.479
YKL40(ng/ml)	All cases(49"MW")	10-55(19)	(12-24(15)	.042
	-ve FHA (24) "MW"	12-50(15)	12-24(15)	0.562
	+ve FHA (25) "MW"	12-55(25)	12-24(15)	0.002

YKL-40: Serum Chitinase3-like protein1, **NICU:** Neonatal Intensive Care Unit, **CRP:** C-reactive protein, **RBCs:** Red Cell Counts, **Hb:** Hemoglobin, **FHA:** Family history of asthma

Table 5: Serum YKL40 Correlation with Laboratory Data

Parameter	R	P
WBCs	0.029	0.842
Neutrophils	0.371	0.009
Platelets	-0.12	0.836
RBCs	-0.084	0.568
Hb	0.161	0.27
CRP	0.089	0.541

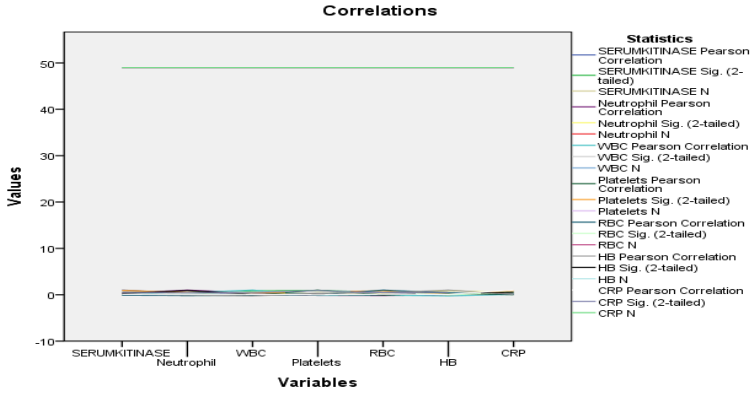

Figure 1: Serum YKL-40 relation to Laboratory Parameters

DISCUSSION

Chitinase -3 like protein-1 YKL-40 is an inflammatory biomarker involved in airway remodeling due to its effect on smooth muscle proliferation [14] and its correlation with sub-epithelial fibrosis and bronchial wall thickness [15,16] Most reports in pediatric patients were described in asthmatic children and obstructive pulmonary diseases [6,7], while little reports were done in wheezy children as primary presentation. The aim of this study to estimate prognostic and possible diagnostic value of YKL 40 in evaluation of severity and type of wheezing which may be reflected on its management plan . No available reports about this marker in infancy period (1 months -2 years . Our cases were divided clinically according to their recurrence, NICU admission, family history of asthma and severity. Mild cases usually treated in OPD and have not been hospitalized and did not require extensive investigation and follow up and were not included in our study. Our cases were age, sex and weight matched with control group (P was 0.15,0.564 and 0.567 respectively).

Wheezy infants showed lower values of Hb (but still in normal range), neutrophil count, serum YKL40 compared to controls (P was: 0.031 ,0.00 and 0.028 respectively) Neutrophil count showed positive correlation with YKL-40. Unfortunately, no available study about serum YKL-40 in wheezing in infancy period. James et al [11] found that preschool children (6-44months) with wheezes has significant higher neutrophil count and serum YKL-40 compared to control. Increased neutrophil in wheezing may results from associated viral infection and pro-inflammatory cytokines associate wheezing [17,18, 19]. In that study [11] serum YKL-40 was significantly higher at acute visit and at 3 months follow up but not at 1 year follow up compared to control. Also, it was increased in infant with acute bronchiolitis and bronchiolitis obliterans compared to control [12]. It was increased in children with asthma, and chronic obstructive pulmonary diseases [20-22]. Positive correlation with neutrophil was found in acute bronchiolitis and preschool children with wheezes was also found [11,12]. YKL-40 is an inflammatory marker released from neutrophils and macrophages at time of infection and inflammation in adults [23,24]. This correlation with neutrophil count possibly reflects relation of the marker to severity of inflammation and consequently clinical condition. Allergen challenges in adults induced increase in YKL 40 in BAL despite unknown trigger did not increase its serum level [25-27]. Correlation of this marker to type and severity of inflammation was observed in previous studies [5,12]. In our study serum YKL140 was higher in cases with family history of asthma compared to cases without family history

(P was 0.003 respectively). This results support that rise in this marker can give clue about type of inflammation. This is supported by lack of significant rise in YKL-40 cases with negative family history of asthma in our study (P was 0.562 respectively). No significant difference in serum YKL40 between critical cases and stable cases (p was 0.513). this results possibly due to small sample size in our study. Knihtilä et al found that serum YKL 140 was linked to small airway function in children with asthmatic symptoms as evidenced by correlation with all baseline impulse oscillometry (IOS) indices and higher value in children with significant higher airway hyper reactivity (AHR) and bronchodilator responsiveness (BDR) [7]. In asthmatic children it was higher than control and higher in acute cases compared with stable cases and correlated positively with severity of acute attack. [28,29] In adults with bronchial asthma it correlated inversely with forced expiratory volume (FEV1) [30]. Also, it increased significantly from mild-moderate to severe asthma and was significantly increased in patients with chronic obstructive lung disease compared with severe asthma [31].

Our study reflects that serum YKL-40 increase significantly in wheezy infant compared to control cases with positive family history of asthma and allergic diseases showed higher values. These results reveal prognostic and diagnostic value of the marker in wheezy infant. Previous studies showed elevation of this marker in other allergic conditions as atopic dermatitis. [32]. Relation of this marker to allergies may be explained by association with genetic mutation CHI3L1. Genetic variation in CHI3L1 influenced serum YKL-40 levels and was associated with increased the risk of asthma, bronchial hyper-responsiveness and reduced lung function [30].

Our study has clinical implication. Elevation of serum YKL-40 in wheezy infant may suspect allergic wheezing and possible later development of asthma. This marker may have role in management of wheezing especially of allergic origin. Inhibition of this marker by k284-6111 reduce skin manifestation in atopic dermatitis in animal model through suppression of lactoferrin and consequently inflammatory cytokines [33].

The limitation of this study: Relatively small sample size. Also, no follow up of wheezing cases to correlate the marker to response of treatment and determine type of wheezes. This may need further study with large number of cases with identification of type of wheezing. and relation to this marker.

CONCLUSION AND RECOMMENDATION

Serum YKL-40 was evaluated in wheezy infants. It was significantly higher in wheezing infants compared to control. Cases with family history of asthma showed higher level of this marker compared with those without family history of asthma. It showed positive correlation with blood neutrophil. These results have diagnostic and prognostic significance regarding infant wheezes.

List of Abbreviation: chitinase-3-Like Protein 1(YKL-40), complete blood count (CBC), C reactive protein (CRP), gastro-esophageal reflux disease (GERD), Neonatal intensive care unit (NICU) Respiratory rate (RR), impulse oscilometry (IOM) , airway hyper reactivity (AHR},bronchodilator responsiveness (BDR).

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