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ORIGINAL ARTICLE

Evaluation of Plasma Gelsolin Level as a Diagnostic Biomarker in Pediatric Pneumonia

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ABSTRACT

Background: The decrease in the level of gelsolin was related to the prognosis and severity of many diseases, such as hyperoxic lung injury, sepsis, bronchopulmonary dysplasia (BPD), and intracranial hemorrhage. **Aim of the work:** The aim of the current study was to study the role of plasma gelsolin level in diagnosis of pneumonia in infant and children. **Methods:** A Prospective Case control study was conducted on 50 subjects whom admitted to the Zagazig University Children Hospital and Microbiology and Immunology Department, Faculty of Medicine in collaboration with Molecular Biology Unit Zagazig Scientific and Medical Research Center during the period from September 2018 to April 2019, the study included 50 participants were divided into 2 groups; Group (I): 40 patients with Pneumonia, and they were classified into 3 subcategories groups (mild - moderate - severe) according to PRESS scorning system and Group (II): 10 apparently healthy subjects as a control group. **Result:** There was a high statistically significant difference between patients and control group as regard hemoglobin level, TLC, CRP and lymphocyte count, there was a statistically significant difference in gelsolin level between patients group and control group. **Conclusion:** gelsolin serum level decrease in pneumonia and can be used as diagnostic and prognostic marker with good statistical performance.

Keywords: Plasma Gelsolin Level, Diagnostic Biomarker, Pneumonia.

INTRODUCTION

Pneumonia is defined as an inflammation of lung tissue due to an infectious agent. Commonly used clinical World Health Organization operational definition which based solely on clinical symptoms (cough or difficulties in breathing and tachypnea). In the developing world the term Lower Respiratory Tract Infection (LRTI) is widely used instead of pneumonia, because of poor access to x-ray and difficulties in radiological confirmation of diagnosis [1].

Many organisms cause pneumonia such as viruses, bacteria, protozoans, and fungi. pneumonia commonly preceded by acute viral bronchitis. Viruses infections with pathogenic microorganisms colonizing nasopharynx. These pathogens including Moraxella catarrhalis, Streptococcus pneumoniae, and Haemophilus influenzae. The Previous colonization of Streptococcus mitis and anaerobic cocci Peptostreptococcus anaerobius could have a protective effect against pathogenic strains [2].

The onset of pneumonia could be sudden or slowly progressive. In most cases the symptoms of pneumonia mimics that of flu or other common lung infections such as bronchitis [3].

Gelsolin is an action-binding plasma protein that has a protective role against tissue injuries. Studies of sepsis have shown that the decrease of plasma gelsolin (pGSN) correlated with elevated circulating levels of actin and pGSN

changes correlated with clinical improvement in pneumonia patients [4].

Gelsolin (GSN) is a calcium dependent actin binding protein predominantly responsible in removal of actin filaments released into circulation upon cell injury. pGSN is secreted in high amount in skeletal muscles and present in blood in high levels at ~ 200 ± 50 ng/ml. pGSN levels decrease by 20-50% in several clinical conditions in humans as well as animals [5].

There are many reviews in the literature about the structure, activation of gelsolin as well as about the mechanism of action severing by gelsolin and about the relation of gelsolin in health and diseases [6, 7].

The aim of the current study was to study the role of plasma gelsolin level in diagnosis of pneumonia in infant and children

PATIENTS AND METHODS

This Prospective Case control study was conducted in the Zagazig University Children Hospital and Microbiology and Immunology Department, Faculty of Medicine in collaboration with Molecular Biology Unit Zagazig Scientific and Medical Research Center during the period from September 2018 to April 2019, the study included 50 participants were divided into 2 groups were divided into 2 groups; Group (I): 40 patients with Pneumonia, and they were classified into 3 subcategories groups (mild - moderate - severe) according to PRESS scorning system and Group (II): 10 apparently healthy subjects as a control group

Written informed consent was taken from participants' parents and the study was carried according to the research ethical committee of Faculty of Medicine, Zagazig University. The study was carried out in due to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria

Both male and female, sever respiratory symptoms such as cough, apnea, dyspnea, tachypnea, fever > 380C, Leucopenia (<4,000/mm3) or leukocytosis (≥15,000/mm3) and ≥10% immature forms (infants ≤ 1 year of age), purulent sputum, Increased espiratory secretions, Changes in the characteristics of sputum and respiratory secretions, wheezing, nasal flaring with retractions in chest wall and grunting, Auscultary findings; ↓ air entry – Ronchi, crepitation, Increased O2 requirements and hypoxemia (Sat <94%) this condition is obligatory for infants ≤1 years old .

Exclusion criteria:

Parent refused to share in the study, Patient with multiple congenital anomalies, RD due to asthma or FB or other causes rather than pneumonia.

The participants were divided into 2 groups:

Group (I): 40 patients with Pneumonia, and they were classified to 3 subcategories (mild - moderate , and sever) according to PRESS scorning system).

Group (II): 10 apparently healthy subjects as a control group.

All participants were subjected to:

Thorough history taking (Personal data, Nutrition history, Family history, Development history and Vaccination history.

Detailed clinical examination including (General examination (vital sign), Anthropometric measurement)

Radiology. Chest X-ray

Laboratory investigations:

Routine Labs: complete blood count with differential cell count, using automated cell counter “Sysmex KX21” supplied by Sysmex Corporation (Japan), with the examination of Leishman–stained peripheral blood smears for differential leucocytes count, Quantitative measurement of the level of C-reactive protein (CRP).

Kidney Function Tests: K, Na, serum creatinine and blood Urea.

Liver Function Tests: AST (Aspartate aminotransferase), ALT (Alanine aminotransferase), total bilirubin and albumin.

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Pediatric Respiratory Severity Score (PRESS)

The data of five components was collected using the PRESS: rate of respiration, wheezing, use of accessory muscles, SpO2 and difficulties of feeding. The use Accessory muscle was defined as visible retraction of one or more intercostal and subcostal muscles. Wheezing was defined by auscultation which performed by experienced pediatricians. SpO2 was assessed as over or below 95%. Difficulties of Feeding were evaluated due to information obtained from the parents. Each component was given 0 or 1 point and the PRESS total score was classified as mild (from 0–1 points)., moderate (from 2–3 points) and severe (from 4–5 points). Rate of respiration was assessed based on the guidelines of American Heart Association.

Plasma Gelsolin Level by ELISA.

Procedure:

1. All reagents and samples were kept in a room temperature (18–25 °C) before use. It was recommended that all standards and samples be run at least in duplicate.
2. 100 ml of each standard and sample into appropriate wells were added. wells and incubate were covered for 2.5 hours at room temperature or overnight at 4 °C with gentle shaking.
3. The solution and wash 4 times with 1x Wash Solution were discarded. Washed by filling each well with Wash Buffer (300 ml) using a multichannel pipette or auto washer. Complete removal of liquid at each step is essential to good performance. After the last wash, remove any remaining Wash Buffer by aspirating or decanting. Invert the plate and blot it against clean paper towels.
4. 100 ml of 1x prepared Biotinylated Detection Antibody to each well were added. Incubated for 1 hour at room temperature with gentle shaking.
5. The solution was discarded. Repeated the wash as in step 3
6. 100 ml of prepared HRP-Streptavidin solution to each well were added. Incubated for 45 minutes at room temperature with gentle shaking
7. The solution was discarded. Repeated the wash as in step 3
8. 100 ml of ELISA Colorimetric TMB Reagent (Item H) to each well were added. Incubated for 30 minutes at room temperature in the dark with gentle shaking
9. 50 ml of Stop Solution (Item I) to each well were added. Readied at 450 nm immediately.

3. STATISTICAL ANALYSIS

Data was analyzed by SPSS program. The significance level was set at ($p<0.05$) and ($P<0.001$) as high significance.

RESULTS

There was no statistically significant difference between cases or control groups regarding age, weight or gender (Table 1). There was a statistically significant difference in pairwise comparison between moderate and severe group regarding age and body weight, but regarding gender, there is no statistically significant difference (Table 2). There was a highly statistically significant difference between patients and control group as regard hemoglobin level, TLC, CRP, and lymphocyte count (Table 3). There was a high statistically significant difference between patients' group and control group regarding gelsolin level (Table 4). There was no statistical non-significant difference between patients with different degrees of severity and plasma gelsolin level (ng/ml) (Table 5). There was a significant correlation with plasma gelsolin among the studied patients, regarding TLC and hemoglobin (Table 6). The best cutoff of gelsolin level in diagnosis of absence of pneumonia was ≥ 619 ng/ml with area under curve 0.951., sensitivity 90%., specificity 82.5%., positive predictive value 56.2% negative predictive value 97.1%, positive likelihood ratio 5.1, negative likelihood ratio 0.1 and accuracy 84% (Table 7). The best cutoff of gelsolin level in diagnosis of moderate

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pneumonia was ≥362.5 ng/ml to <371.5 ng/ml with area under curve 0.556, sensitivity 60%, specificity 56%., positive predictive value 44%., negative predictive value 70%., positive likelihood ratio 1.4, negative likelihood ratio, 0.7 and accuracy, 57.5% (Table 8). The best cutoff of gelsolin level in diagnosis of mild pneumonia was ≥ ≥371.5 ng/ml to <619 ng/ml with area under curve 0.628, sensitivity 60%, specificity 60%, positive predictive value 47.4%, negative predictive value 71.4%, positive likelihood ratio 1.5, negative likelihood ratio 0.7 and accuracy 60% (Table 9). The best cutoff of gelsolin level in diagnosis of mild pneumonia was 194ng/ml with area under curve 0.27, sensitivity 70%, specificity 20%, positive predictive value 22.6%, negative predictive value 66.7%, positive likelihood ratio 3.5, negative likelihood ratio 0.67 and accuracy 32.5% (Table 10).

Table (1): Comparison between the studied group regarding demographic data :

	Group I (40)		Group II (10)		Z	P
	Median (range)		Median (range)			
Age (months)	**9.36 (1.5 – 120)**		**11 (4 - 24)**		**-1.825**	**0.068**
Weight (kg)	**6 (4 – 30)**		**9.5 (4 – 13)**		**-1.562**	**0.118**
	N = 40	**%**	**N =10**	**%**	**X2**	**P**
Gender:						
Male	**28**	**70**	**7**	**70**	**0**	**1**
Female	**12**	**30**	**3**	**30**		

*p<0.05 is statistically significant Z mann whitney test

Table (2): Comparison between the patients with different severities regarding demographic data:

	Mild		Moderate		Severe		KW	P
	Median (range)		Median (range)		Median (range)			
Age(month)	5 (4-24)		9(2-120)		4.5(1.5-9)		6.676	0.035*
Pairwise comparison	P1	0.2	P2	0.043*	P3	1		
Weight (kg)		6 (4-13)		7(4-30)		5.8(4-7.5)	6.944	0.031*
Pairwise comparison	P1	0.701	P2	0.025*	P3	0.349		
	N	**%**	**N**	**%**	**N**	**%**	**X2**	**P**
Gender:								
Male	11	73.3	11	73.3	6	60	0.635	0.728
Female	4	26.7	4	26.7	4	40		

**p<0.05 is statistically significant, P1 difference between mild and moderate groups; P2 difference between moderate and severe group; P3 difference between mild and severe group*

Table (3): Comparison between the patients with different severities regarding complete blood picture, CRP:

	Group I (40)		group II (10)		t	p
	Mean±SD	**Range**	**Mean±SD**	**Range**		

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	Group I (40)		group II (10)		t	p
Hemoglobin ((g/dl)	10.29 ± 1.46	7.6 – 13.2	12.3 ± 1.1	11 - 14	-4.067	<0.001**
TLC (X10^3/uL)	14.1±4.55	7.3 – 28	8.7 ± 1.5	6 - 11	6.258	<0.001**
	Mean±SD	**Median (range)**	**Mean±SD**	**Median (range)**	**Z**	
Neutrophil (X10^3/uL)	6.1± 3.26	5 (1.7 – 16.7)	5.3 ±1.1	5.5 (4–7)	-0..037	0.971
Lymphocytes (X10^3/uL)	5.96±2.31	5.5(2-12)	3.5 ± 0.97	4 (2 – 5)	-3.308	0.001**
Platelet count (X10^3/uL**)**	376.7±128.1	342.5 (220-725)	312 ± 75.84	300 (250 – 450)	-1.504	0.133
CRP Mg/l	92.98±112.7	80.19 (7 – 445)	3.3 ± 1.25	3 (1 – 5)	-4.85	<0.001**

**p≤0.001 is statistically highly significant

Table (4): Comparison between the studied group regarding plasma gelsolin level:

	Case group	Control group	Z	P
	Median(range)	**Median(range)**		
Plasma gelsolin level ng/ml	**362.5 (58-781)**	**719.5(615 – 748)**	**-4.378**	**<0.001****

**p≤0.001 is statistically highly significant

Table (5): Comparison between the patients with different severities regarding plasma gelsolin level:

	Mild	Moderate	Severe	KW	p
	Median (range)	Median (range)	Median (range)		
Plasma gelsolin level ng/ml	427 (119-716)	378 (105-781)	289 (58-434)	4.82	0.09

Table (6): Linear stepwise regression analysis of variables independently associated with plasma gelsolin level:

	Unstandardized Coefficients		Standardized Coefficients	t	P
	B	Std. Error	B		
TLC **(**X10^3/uL**)**	-15.321-	6.195	-0.326-	-2.473-	0.017*
HB g/dl	37.073	17.963	0.272	2.064	0.045

DISCUSSION

Pneumonia is now considered to be the leading infectious cause of mortality worldwide and one of the most common infections contributing significantly to the burden of antibiotic consumption. It is classified as either community-acquired or nosocomial, according to the environment from which the patient contracted the infection [8]. Gelsolin is a calcium-dependent, multifunctional actin regulatory protein circulating in the plasma of healthy humans. Gelsolin is primarily involved in the rapid severing and removal of actin filaments released from dead cells into the blood stream. In addition, gelsolin binds to a variety of proinflammatory and bioactive molecules, including lysophosphatidic acid, sphingosine 1-phosphate, fibronectin, and platelet-activating factor in the body. Moreover, gelsolin acts as a mediator of many physiological functions, including wound-healing, neurologic development, cancer progression and angiogenesis [9].

The current study revealed that there was no statistically significant difference between patients and control groups regarding age, weight and gender.

The current study showed that there was a high statistically significant difference between patients and control group regarding hemoglobin level and TLC.

Harris et al. [10] also showed in a study done among Ecuadorian children, they studied air pollution as a risk factor for the infections of acute lower respiratory tract. They demonstrated that children with anemia were at high risk of acute respiratory infection hospitalization compared to healthy children. They explained their results by that the deficit of central pathophysiological in acute lower respiratory infections is poor tissue oxygenation and anemia independently decrease delivery of oxygen.

Our results revealed that there was no statistical significant difference between patients with different severities regarding CBC findings and acute phase reactants, which in agreement with the study of Aronsky and Haug [11] who found that although the clinical parameters are needed for the evaluation of the PSI, the variables are not obtained for every pneumonia patient as part of clinical care in the emergency department indicating that no difference between different degrees of pneumonia and clinical and laboratory data.

The current study found that there was a statistically significant difference between patient groups with different degrees of severity regarding gelsolin levels. Which in agreement with the study of Smith et al. [12] who reported that patients with pneumonia and febrile seizures also had lower gelsolin levels, which indicates that factors other than hemolysis can lower the concentration of gelsolin.

Our results revealed that there was no statistical significant difference between patients with different degrees of severity and plasma gelsolin level. Which in agreement with the study of Oikonomou et al. [13] who reported that gelsolin was overexpressed in the samples of patient's tissue with idiopathic pulmonary fibrosis and fibrotic non-specific interstitial pneumonia but in the other forms of idiopathic interstitial pneumonias. These results suggested that the expression of gelsolin could be protective or harmful in different diseases due to the several pathogenic mechanisms.

On the other hand, the present study revealed that there was a statistically significant positive correlation between plasma gelsolin level and hemoglobin level while there was significant negative correlation between it and TLC.

Additionally, our results revealed that the best cutoff of gelsolin level in diagnosis of absence of pneumonia is ≥ 619ng/mL with area under curve 0.951, sensitivity 90%, specificity 82.5%, positive predictive value 56.2% negative predictive value 97.1%, positive likelihood ratio 5.1, negative likelihood ratio 0.1 and accuracy 84%.

While the study of Kose et al. [14] reported that due to the ROC analysis for sepsis and pneumonia, the area under curve was 0.86 for

PGN.A PGN level cut-off of 1,006 ng/mL yields 75% sensitivity and 100% specificity.

Hu et al. [15] who demonstrated that despite the lower significance of plasma gelsolin levels in patients with RA, its potential clinical application in the diagnosis of RA and disease activity assessment was limited since there was no correlation between plasma gelsolin levels and RA disease activity score 28 (DAS28) was noticed.

The present study assessed the sensitivity and specificity of gelsolin for detection of mild and moderate pneumonia where it found that the best cutoff of point of gelsolin level in diagnosis of moderate pneumonia is ≥362.5 to <371.5 with area under curve 0.556, sensitivity 60%, specificity 56% and the best cutoff of gelsolin level in diagnosis of mild pneumonia is ≥371.5 to <619 with area under curve 0.628, sensitivity 60%, specificity 60 which agreed with the results of Kim et al. [16] study.

CONCLUSION

Gelsolin serum level decrease in pneumonia and can be used as diagnostic and prognostic marker with good statistical performance.

Conflict of interest

The authors of this manuscript declare no relevant conflicts of interest.

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