

Pentraxin 3: A Potential Novel Predictor for Neonatal Pulmonary Hypertension

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Abstract

Citation: El Wakeel MA, Sabry RN, El-kassas GM, Abd El-Gaffar SA, El batal WH, Galal EM, Azmy A, Awadallah E. Pentraxin 3: A Potential Novel Predictor for Neonatal Pulmonary Hypertension. Open Access Maced J Med Sci. 2019 Aug 15; 7(15):2424-2427. <https://doi.org/10.3889/oamjms.2019.638>

Keywords: Pentraxin 3; Pulmonary hypertension; Neonates; Congenital heart disease

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Received: 23-Jul-2019; **Revised:** 01-Aug-2019; **Accepted:** 03-Aug-2019; **Online first:** 14-Aug-2019

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Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

BACKGROUND: Persistent pulmonary hypertension of the newborn (PPHN) is a serious neonatal problem which has a high mortality rate even with advanced modes of mechanical ventilation. Pentraxin 3 is one of the long pentraxins, which plays an essential role in regulation of cell proliferation and angiogenesis.

AIM: This study aims to assess serum pentraxin 3 levels in neonates with pulmonary arterial hypertension and compare them in those who have other congenital heart diseases and healthy neonates. Also, we intended to evaluate serum levels of CRP as a mediator of inflammation in the studied groups.

METHODS: The study is a case-control study. Cases were recruited from El Galaa Teaching Hospital, classified into three groups; each group had thirty cases. The first one: cases with pulmonary hypertension (PHT), the second one: cases with congenital heart diseases (CHD) without pulmonary hypertension and the third group included healthy neonates. All participants were subjected to full history taking and full clinical examination. Diagnosis of congenital heart disease and pulmonary hypertension was made according to echocardiographic findings by pediatric cardiologist using echocardiography machine. Laboratory investigations included measurement of serum pentraxin 3, Routine CBC, CRP.

RESULTS: This study found that the mean serum pentraxin 3 in PHT neonates was significantly higher than that of the control and CHD neonates ($p \leq 0.001$, $p = 0.02$ respectively). Also, the mean Pentraxin3 of the CHD neonates was significantly higher than that of the control ($p = 0.06$). Also, the mean CRP of the PHT neonates was significantly higher than that of the control ($p = 0.01$). Regression analysis showed that Pentraxin3 was the main predictor of PAP ($P = 0.01$).

CONCLUSION: Serum pentraxin 3 is significantly elevated in neonates with pulmonary hypertension, so measurement of pentraxin 3 levels in neonates may be valuable as a predictor for pulmonary hypertension in neonates.

Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is considered a serious condition that appears in the neonatal period, which is always complicated by high morbidity and mortality. It is due to that the neonate fails to make a postnatal change from a high resistance fetal pulmonary circulatory state to a low resistance pulmonary circulation [1]. This low pulmonary blood flow secondary to increased pulmonary vascular resistance counteract potent gas

exchange in the lungs prompting severe respiratory distress and decreased blood oxygen level in the neonate [2]. Data suggested that PPHN happens in 1-2 infants / 1000 live births [3]. A recent study was performed in Egypt found that PPHN was found in 5% of the studied population [4]. The neonate has PPH is usually term or late-preterm and usually is not associated with congenital anomalies. Affected neonate complains shortly after birth with severe shortness of breath that needs mechanical ventilation [5]. In spite of different management procedures such as nitric oxide, aggressive mechanical ventilation and

extracorporeal membrane oxygenation (ECMO), the mortality rate for this disease is about 10-20% of affected neonates [6]. This aggressive treatment and occurrence of hypoxemia expose these neonates to have long-term sequelae including chronic lung disease, seizures, and neurological developmental problems [7].

Pentraxin 3 is a subclass of long pentraxins which is synthesised by fibroblasts, smooth muscle cells and endothelium. Also, innate immune cells during inflammation secrete pentraxin 3. It plays a vital role in cell proliferation regulation and angiogenesis [8]. Serum levels of CRP are mediators of inflammation [9]. CRP is considered one of the short pentraxin which is produced in the liver in case of systemic inflammation [10].

Using echocardiography has further expanded as an adjunct to physical examination to improve diagnostic accuracy and risk of cardiac diseases [11].

Fractional shortening (FS) is used to assess left ventricular dysfunction. It simply measures the degree of shortening of the diameter of left ventricle between end-diastole and end-systole. It is one of the most important measures in functional echocardiography [12].

The aim of this study was to evaluate serum pentraxin 3 levels in neonates with pulmonary arterial hypertension and compare them with those who have other congenital heart diseases and healthy neonates. Also, we intended to evaluate serum levels of high sensitive-CRP (hs-CRP), as a mediator of inflammation in the three studied groups.

Material and Methods

This study is a case-control study. Studied cases were recruited from El Galaa Teaching Hospital. It was approved by the local ethical committee of the National Research Center, and parental written informed consent was obtained from all study participants. Participants were classified into three groups; each group had thirty cases. The first one: cases with pulmonary hypertension, the second one: cases with congenital heart diseases with normal pulmonary pressure and the third group included healthy neonates. They were age, sex and gestation matched with neonates of other three groups. All participants were subjected to full history taking and full clinical examination. Demographic and clinical data such as age, sex, birth weight, and gestational age were documented in all participants.

Diagnosis of congenital heart disease, pulmonary hypertension and other cardiac measurements including fractional shortening (FS)

were made according to echocardiographic findings performed by pediatric cardiologist using echocardiography machine (Sonosite®, USA, probe 5–8 Hz) [13]. Neonates meeting any of the following criteria were excluded from the study: diagnosis of proven sepsis by positive blood culture, disseminated intravascular coagulation, severe hypoxic respiratory failure, low Apgar score, non-congenital heart diseases (e.g., endocarditis) or maternal history of chorioamnionitis.

Venous blood sample (2 ccs) was taken from each participant and serum was separated and stored at -30 until collection of all the samples then laboratory investigations were done. Laboratory investigations included measurement of serum pentraxin 3, Routine CBC. Serum Pentraxin 3 (PTX3) level was assessed by enzyme-linked immunosorbent assay (ELISA) following instructions of the kits purchased from Sino Gene Clon Biotech Co., Ltd. Catalog No: SG-10465. Serum hs-CRP levels were determined with an enzyme-linked immunosorbent assay (ELISA) technique using commercial kits (BioCheck, Inc 323 Vintage Park Drive Foster City, CA 94404) and the sensitivity of detection level was 0.01 mg/dl.

Statistical analysis

Data entry was carried out on excel sheet and analysis was done using SPSS software program version 22 (SSPS Inc., Pennsylvania, USA). Mean \pm SD was used to present quantitative data. T-test was done for comparison between two means. Pearson's correlation analysis was performed to estimate the association between variables. Linear regression analysis was performed to identify the main predictors of PAP. P-value was considered statistically significant when P was < 0.05.

Results

Subjects in this study were classified into three groups; each group had thirty subjects.

Table 1 shows the demographic and laboratory data of the studied groups. Comparison between PHT, CHD without pulmonary hypertension and control groups as regards different variables were shown in Table 1. No significant difference was found between the studied groups as regards age, GA and FS. As regards laboratory investigations, it was found that the mean CRP of the PHT group was significantly higher than that of the control ($p = 0.01$). Also, serum pentraxin 3 in PHT group was significantly higher compared to the control and CHD groups ($p \leq 0.001$, $p = 0.02$ respectively). The mean Pentraxin3 of the CHD group was significantly higher in comparison to

controls ($p = 0.06$).

Table 1: Demographic and Echocardiographic data in the studied groups

| Variable | PHT (Mean \pm SD) | CHD (Mean \pm SD) | Control (Mean \pm SD) | P1 | P2 | P3 |
|--------------------------|------------------------|------------------------|----------------------------|----------------|--------------|-------|
| Age (days) | 3.95 \pm 1.59 | 3.97 \pm 2.36 | 4.37 \pm 0.93 | 0.19 | 0.97 | 0.39 |
| Weight (Kg) | 2.64 \pm 0.71 | 2.97 \pm 0.44 | 2.85 \pm 0.53 | 0.171 | 0.03* | 0.34 |
| GA (weeks) | 37.03 \pm 1.42 | 37.30 \pm 1.37 | 37.53 \pm 1.72 | 0.112 | 0.42 | 0.46 |
| PAP (mm Hg) | 62.15 \pm 14.48 | 28.7 \pm 7.3 | | | ≤ 0.001 | |
| FS (%) | 40.38 \pm 3.18 | 41.10 \pm 2.06 | | | 0.28 | |
| CRP (mg/dl) | 2.88 \pm 0.91 | 2.53 \pm 0.90 | 2.40 \pm 0.50 | 0.01* | 0.12 | 0.48 |
| Pentraxin 3 (μ g/l) | 7.60 \pm 2.17 | 6.38 \pm 2.20 | 5.53 \pm 0.84 | $\leq 0.001^*$ | 0.02* | 0.06* |

P1: PHT Vs Control P2: PHT Vs CHD P3: CHD Vs Control; PHT: neonates with pulmonary hypertension PAP: Pulmonary artery pressure; CHD: Neonates with congenital heart disease without pulmonary hypertension; GA: Gestational age FS: Fractional shortening; * $P < 0.05$, the relationship is significant.

Multiple correlations were calculated between serum pentraxin 3 and all other variables. They showed that PAP was positively correlated with serum pentraxin 3 (as shown in Figure 1) and FS ($p = 0.009$, $p = 0.011$ respectively).

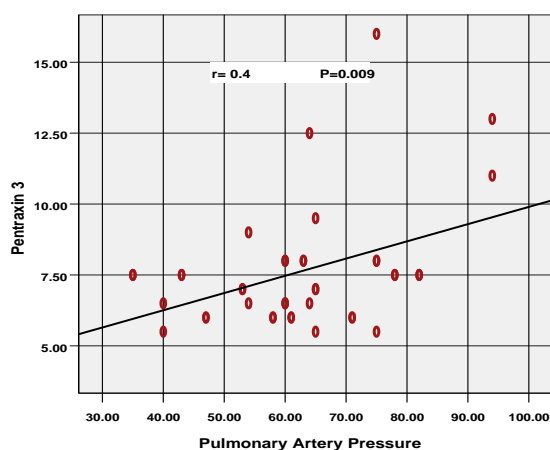


Figure 1: Correlation between PAP and serum pentraxin 3

To show the influence of pentraxin 3 and CRP on PAP as a dependent factor, we did linear regression analysis. This analysis showed that Pentraxin3 was the main predictor of PAP ($P = 0.01$), as shown in Table 2.

Table 2: Predictive factors for increased PAP in the PHT group as estimated by linear regression

| Model | Unstandardized Coefficients | | Standardised Coefficients | t | Sig. |
|--------------|-----------------------------|------------|---------------------------|-------|------|
| | B | Std. Error | Beta | | |
| (Constant) | 39.727 | 11.163 | | 3.559 | .001 |
| 1 Pentraxin3 | 2.742 | 1.011 | .410 | 2.712 | .010 |
| CRP | .550 | 2.405 | .035 | .229 | .820 |

* $P < 0.05$, the relationship is significant.

Discussion

Pulmonary hypertension is one of the serious conditions in neonates which may be idiopathic, associated with congenital heart disease or lung

disease and postoperative. In this study, it was found that the mean serum pentraxin 3 in neonates with PHT was significantly higher than that of the control and neonates with other CHD with no PHT. Also, the mean Pentraxin 3 of the later group was significantly higher than that of the control. This was in agreement with several studies which found that the mean serum pentraxin 3 in neonates with PHT was significantly higher than that of the control and neonates with other CHD [14], [15], [16]. Also, we found that the mean hs-CRP of the PHT neonates was significantly higher than that of the control.

Similarly, other studies found that hs-CRP was significantly elevated in PHT patients. They added that inflammation is a contributing factor to the progression of pulmonary hypertension [15], [16], hs-CRP is one of the short pentraxins and is strongly released secondary to inflammation. To clarify our results, multiple correlations were calculated between serum pentraxin3 and all other variables. It showed that PAP was positively correlated with serum pentraxin 3. This may be explained by that pentraxin 3 has a role in angiogenesis and vascular diseases. It is secreted at sites of inflammation not only by endothelial cells but also by macrophages and monocytes infiltrating sites of inflammation that happens in pulmonary hypertension [17]. No correlation was found between serum pentraxin 3 and hs-CRP as found in previous study [15]. To show the influence of pentraxin 3 and CRP on PAP as a dependent factor, we did linear regression analysis. This analysis showed that Pentraxin3 was the main sensitive biomarker of PAP than hs-CRP. This is similar to findings of Tamura et al., who added that hs-CRP is increased to a significant degree in the PAH group. This study also found that PAP was positively correlated with FS [15].

In conclusion, serum pentraxin 3 is an important sensitive biomarker of pulmonary artery pressure. It is elevated in pulmonary artery hypertension, so measuring serum pentraxin3 might be useful in prediction and progression of pulmonary artery hypertension in neonates.

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