Cancer Cell Research 25 (2020) 666-670

Available at http:// www.cancercellresearch.org ISSN 2161-2609

Study on the relationship between PCT, D-dimer, NT-proBNP levels, pulmonary function and pulmonary hypertension related to asthmatic disease in children

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Abstract: **To investigate relationship of PCT, D-dimer, NT-ProBNP level and pulmonary function in asthmatic children with pulmonary arterial hypertension. Eighty children with asthmatic diseases were elected from admitted inpatient during October 2017 to September 2019, according to whether combined pulmonary hypertension patients can be divided into pulmonary artery hypertension group (30 cases) and non pulmonary arterial hypertension group (50 cases). PCT, D-dimer and NT-ProBNP were detected and compared between the two groups. The Pulmonary function (VT/kg, Ti/TE, TpTe/TE, Vptef/VE) were detected and compared between the two groups. There was a positive correlation between NT-ProBNP, D-dimer and PASP. The levels of PCT, D-dimer and NT-ProBNP in pulmonary arterial hypertension group were higher than those in non pulmonary arterial hypertension group (P<0.05). The levels of MV, VT/kg, Ti/TE, TpTe/TE and Vptef/VE in the pulmonary arterial hypertension group were lower than those in the non pulmonary arterial hypertension group (P<0.05). There was a positive correlation between NT-ProBNP, D-dimer and PASP. The levels of PCT, D-dimer and NT-ProBNP in the pulmonary arterial hypertension group were significantly higher than those in the non pulmonary arterial hypertension group. There are different degrees of small airway obstruction in asthmatic diseases. The degree of pulmonary function decline in pulmonary arterial hypertension group was more obvious than that in non pulmonary arterial hypertension group.**

Keywords: Asthmatic disease; Pulmonary arterial hypertension; Pulmonary function; Procalcitonin; D-dimer; Nterminal-proB type natriuretic peptide

Received 15 December 2019, Revised 26 January 2020, Accepted 28 January 2020

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1. Introduction

Asthmatic disease is a kind of comprehensive respiratory system disease with the main clinical manifestations of repeated coughing and wheezing. It has the characteristics of complex etiology, repeated attacks and difficult to recover. Asthmatic diseases in children include asthma, asthmatic bronchitis, bronchiolitis, bronchiolitis obliterans, bronchopulmonary dysplasia, protracted bacterial bronchitis and other diseases. Recently, it has been found that the incidence of asthmatic diseases is increasing, among which asthma has become one of the most common chronic respiratory diseases affecting about 200 million patients in the world, including children[1]. A group of studies found that more than 50% of asthma patients still have symptoms that have not been controlled[2]. Repeated wheezing can cause different degrees of hypoxia. Long-term hypoxia can cause pulmonary vasospasm, proliferation of pulmonary vascular cells, organization of pulmonary arterioles, continuous increase of pulmonary circulatory resistance, and eventually lead to pulmonary arterial hypertension(PAH). The continuous increase of pulmonary artery pressure leads to the increase of right ventricular filling pressure, thickening of right ventricular cardiomyocytes and myocardial fibrosis. It seriously leads to the dysfunction of right ventricular systolic and diastolic function[3]. Pulmonary hypertension can occur at different ages in childhood, which is a serious threat to children's health. The clinical manifestations of pediatric PAH are not typical. It is easy to be missed and misdiagnosed in the early stage. Once clinical manifestations appear, the disease often develops to a more serious degree, and the disease progresses rapidly, and the treatment effect is not ideal. To investigate the relationship between PCT, D-dimer, NT proBNP levels and pulmonary function in children with asthma related pulmonary hypertension, and to screen children with pulmonary hypertension early to guide clinical treatment, we finished this research work.

2. Data and methods

2.1. General information

80 children with asthmatic diseases were selected from the inpatient department of our hospital, including 45 men and 35 women, aged from 2 months to 4 years and 2 months, with an average age of

(1.32±0.63) years, a body mass of (11.5±1.3) kg and a height of (80.9 ± 5.4) cm, from October 2017 to September 2019. According to the pulmonary artery systolic pressure(PASP) ⩾ 25mmhg, 30 cases were divided into pH group and 50 cases were divided into non pH group. The right of informed consent of the guardian and the authorizer of the child was respected, the informed notice was signed and approved by the ethics committee of the hospital. There was no significant difference between the two groups (P>0.05).

2.2. Inclusion and exclusion criteria

All the children's clinical symptoms meet the criteria of the Chinese Medical Association for the diagnosis of children's asthmatic diseases. The clinical manifestations usually include cough, wheezing, suffocation, expiratory wheezing sound and other related symptoms in the auscultation of lung, excluding tuberculosis infection, foreign body in bronchus, malnutrition and congenital heart disease. The systolic pressure of pulmonary artery was measured by Doppler echocardiography. When the systolic pressure of pulmonary artery was ⩾25mmhg, the patients were divided into PH group and non PH group according to the results of PASP.

2.3. Inspection method

Venous blood was collected within 24 hours, the D-D level of plasma was measured by automatic hemagglutination instrument, and the NT-proBNP and PCT levels were measured by electrochemiluminescence.

Lung function was measured, body weight and height were measured, and tidal inhalation was used. Every child should be tested at least twice to confirm the accuracy of data and record all parameters.

2.4. determination of PASP by ultrasonic Doppler

PASP was measured by the estimation method of valve regurgitation pressure difference, and the maximum tricuspid regurgitation velocity was displayed by color Doppler. According to Bernoulli equation of physics, calculate△P and estimate PASP (PASP-RAP +△P, rap is right atrial pressure;△P = 4v2, V is the maximum velocity of tricuspid regurgitation).

2.5. SPSS 21.0

Statistical software was used for statistical processing, and was used for measurement data. T-test was used to determine the significance of the difference between the two groups, with α=0.05 as the test level.

3. Results

The results of PCT, D-dimer and NT-proBNP in pH group and non pH group were higher than those in non pH group (P < 0.05), Table 1.

Pulmonary function test results: the ratio of inspiratory time (TI) to expiratory time (TE, Ti/TE), the ratio of time to peak tidal volume (TPEF) to total expiratory time (TE, TPEF/TE), the ratio of volume to peak volume Results: the levels of VT/kg, Ti/TE, TPEF/TE and VPEF/VE in pulmonary hypertension group were lower than those in non pulmonary hypertension group, and the difference was statistically significant (P < 0.05), Table 2.

The linear correlation between NT-proBNP, D-dimer and PASP was positive correlation by linear correlation analysis, and the difference was statistically significant. Table

Table 1. Comparison of PCT, D-dimer and NT-ProBNP levels in children with and without pulmonary hypertension ($\bar{X}$±s)

group	cases	PCT(ng/ml)	D-D(mg/L)	NT-ProBNP(pg/ml)
PH	30	0.66±0.30	1.84±1.50	374.77±199
nonPH	50	0.59±0.32	0.47±0.29	84.72±52.57
t		3.01	-4.92	-7.79
p		*P<0.05*	*P<0.05*	*P<0.05*

Table 2. Comparison of pulmonary function between children with and without pulmonary hypertension($\bar{X}$±s)

group	cases	VT/kg(ml/kg)	TI/TE(%)	TPEF/TE(%)	VPEF/VE(%)
PH	30	7.01±2.33	0.66±0.06	16.72±0.91	20.29±4.87
nonPH	50	8.33±0.33	0.73±0.01	27.70±2.50	28.70±1.46
t		4.50	3.78	-3.49	-5.95
p		*P<0.05*	*P<0.05*	*P<0.05*	*P<0.05*

Table 3. NT-ProBNP, D-dimer and PASP linear correlation

project	PASP	
	r	*p*
NT-ProBNP	0.416	*P<0.05*
D-dimer	0.448	*P<0.05*
PCT	-0.210	*P>0.05*

4. Discussion

PH is defined as the combination of mPAP of ⩾25 mmHg at rest, end-expiratory pulmonary artery wedge pressure (PAWP) of >15 mmHg, and pulmonary vascular

resistance (PVR) of >3 Wood units (WU). A study found that the prevalence of PAH in children was 3.7/1 million [5]. Echocardiography is the most important noninvasive method for screening pediatric pH. Right cardiac catheterization is the "gold standard" for the diagnosis of pulmonary hypertension. In addition to diagnosing pulmonary hypertension, echocardiography is also used to evaluate the severity and prognosis of pulmonary hypertension. PAH is one of the serious complications of various cardiopulmonary diseases, and its clinical effect is not ideal. Clinicians are eager to screen patients with pulmonary hypertension early, treat them early and improve their prognosis through simple and noninvasive examination.

BNP is mainly synthesized by ventricular myocytes, which has diuretic, natriuretic and vasodilator effects, and can improve ventricular diastolic function. NT-proBNP is an inactive peptide produced in the process of BNP formation, and it is generated with bnp1:1 and exists in the blood circulation. It has high content, long half-life, relatively stable concentration, high sensitivity and negative predictive value in the assessment of pulmonary hypertension [6]. Leuchte [7] has confirmed that NT-proBNP level can be used as a reference index to evaluate the level of pulmonary artery pressure in patients with pulmonary diseases. It has also been shown that NT-proBNP levels are positively correlated with PASP and with the severity of right ventricular dysfunction. NT-proBNP was used as a factor in the assessment of pulmonary hypertension in the 2015 European heart and respiratory Association pulmonary hypertension guideline [8]. The results showed that the level of NT-proBNP in pH group was significantly higher than that in non pH group. This is probably due to the increase in pulmonary artery pressure due to hypoxia and carbon dioxide retention and the release of NT-ProBNP after stimulation of the right ventricle. Linear correlation analysis showed that NT-proBNP level was positively correlated with PASP, and the difference was statistically significant. The results of this study were consistent with the relevant literature reports.

D-dimer is a kind of specific degradation product produced by fibrinolytic enzyme hydrolysis of fibrin. When the fibrinolysis is high and hypercoagulable, the level of D-dimer in blood increases. The acute exacerbation of the disease often results from infection, hypoxia, CO_2 retention, and other factors, which result in impaired vascular endothelial function and abnormal coagulation function, thereby raising the level of D-Dimer. Zhao Yanxia [9] found that in the acute exacerbation stage of COPD, with the increase of PASP, D-dimer increased, while with the decrease of PO_2 and the increase of PCO_2, and the abnormal coagulation function was related to hypoxia and hypercapnia. Hypoxia can cause the compensatory increase of red blood cells, make the blood in hypercoagulable state, induce thrombosis, promote the release of inflammatory cytokines, accelerate thrombosis, and also cause the increase of pulmonary artery pressure, leading to cardiopulmonary failure [10-11]. There was a positive correlation between D-dimer and PASP[11]. In this study, the level of D-dimer in pH group was significantly higher than that in non pH group, and the difference was statistically significant. Therefore, D-dimer can predict the diagnosis of pH.

PCT is a kind of procalcitonin precursor. When bacteria or fungi are infected, the level of PCT increases significantly in 2-3 hours, but not in virus infection. Therefore, PCT is often used to identify systemic infection and noninfective inflammation, and it is related to the severity of the patient's condition [12]. Domestic studies have found that the PCT level of patients with acute exacerbation of COPD and pulmonary hypertension is higher than that of the control group, and with the increase of pulmonary artery systolic pressure, the level of procalcitonin has a rising trend, which may be related to the severity of systemic inflammatory response and secondary infection. When the respiratory tract is repeatedly infected, it will lead to congestion, edema, denaturation and necrosis of bronchial mucosa cells, increase of sputum and poor drainage, etc., which will aggravate hypoxia. In addition, hypercapnia will aggravate pulmonary hypertension and form a vicious circle [13]. The results of this study showed that the PCT level of pH group was higher than that of non pH group, the difference was statistically significant, the linear correlation analysis showed that PCT was negatively correlated with PASP. The insufficient

sample size of this study may lead to the deviation of the results, and the correlation between PCT and PASP needs to be further confirmed.

In asthmatic children, due to the increase of secretion of mucous glands, airway stenosis often causes dyspnea. The detection of Tidal Pulmonary function can objectively evaluate the characteristics of airway obstruction in asthmatic children, so as to assist in the diagnosis of asthmatic diseases [14]. Scholars have found that TPEF/TE and VPEF/VE are the main indicators of small airway obstruction. The heavier the airway obstruction, the lower the ratio [15-16]. The results showed that VT/kg [(7.01 ± 2.33) ml/kg], Ti/TE [(0.66 ± 0.06)%], TPEF/TE [(16.72 ± 0.91)%], VPEF/VE [(20.29 ± 4.87)%] in pH group were lower than those in non pH group, and the difference was statistically significant. Huang Haizhong[3] showed that the children with asthma disease caused pulmonary hypertension and right heart dysfunction in the acute stage of attack. The heavier the degree of asthma, the more obvious the pulmonary hypertension and right heart involvement. PaO_2 in asthmatic children was significantly lower than that in the control group, while $PaCO_2$ was significantly higher. The higher the level of $PaCO_2$, the more severe the degree of hypoxia, the more severe the degree of pulmonary vasospasm and arteriolar organization, and the more severe the degree of pulmonary hypertension, thus affecting the right ventricular systolic and diastolic function [17-19].

5. Conclusion

The results of this study are similar to those of literature. The levels of PCT, NT-proBNP and D-dimer in pH group are higher than those in non pH group. NT-proBNP, D-dimer and PASP are positively correlated. NT-proBNP and D-dimer can be used as reference indexes to reflect the progress of children's disease. In the study group, there were different degrees of small airway obstruction, and the pulmonary function indexes in the pulmonary hypertension group were significantly reduced. TPTEF/TE and VPEF/VE are important indexes to reflect the degree of respiratory tract damage. This method is safe, noninvasive, simple and easy to use. It is a reliable and sensitive reference index to evaluate the respiratory function of infants. The clinical manifestations of PAH in children are non-specific, not easy to be found in the early stage, and easy to be missed and misdiagnosed. Clinicians are eager to select simple, noninvasive and accurate methods to screen pulmonary hypertension, so as to guide clinical early detection, early diagnosis and early treatment, and provide reference for improving the cardiopulmonary function of children.

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