Comparison on Serum Levels of Procalcitonin of Children with Viral and Bacterial Infection

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Objective To compare and analyze serum levels of procalcitonin (PCT) of children with viral and bacterial infection and probe into the importance of determining the level of serum PCT in the diagnosis of bacterial infection in order to provide evidences of the clinical use of antibiotics.

Methods A total of 85 cases of children with an average age of 8.9 years (10 months -12 years) were enrolled in this study, 53 cases were with viral infection and 32 cases with bacterial infection. We determined serum levels of PCT by semi-quantitative solid phase immunoassay, and the serum levels of PCT were divided into four grades as $<0.5 \mu\text{g/L}$, $\geq 0.5 \mu\text{g/L}$, $\geq 2.0 \mu\text{g/L}$ and $\geq 10 \mu\text{g/L}$ for χ^2 test and Ridit analysis.

Results The serum level of PCT of the group with bacterial infection were significantly higher than that of the group with viral infection ($P < 0.001$). The sensitivity of diagnosis of bacterial infection in children with determination of serum levels of PCT was 87.50% while the specificity was 92.13%, and positive predictive value was 73.68% while negative predictive value was 91.49%, and positive likelihood ratio was 4.65 while negative likelihood ratio was 0.15, and the diagnostic accuracy was 83.53%.

Conclusions Serum PCT is a bacterial sensitive marker of bacterial infection in children, and the determination of the level of serum PCT is helpful for the diagnosis of bacterial infection, which can also be a basis for the use of antibiotics.

Key words: Viral infection; Bacterial infection; Procalcitonin; Children

Fever of unknown origin is a common clinical problem in pediatrics, for which infection is one of the main reasons. Antibiotics were often used blindly before making a definite diagnosis, which may result in the overuse of antibiotics and resistance of bacteria, and increase the financial burden of the children's family. So it is a problem to be solved urgently that choosing a fast and effective experimental method to judge and classify the reasons of infection, thus provide the basis for the use of antibiotics. This article aimed to explore the importance of the determination of the serum levels of PCT in differential diagnosis for children with viral or bacterial infection.

PATIENTS AND METHODS

Patients

Eighty-five cases of children with an average age of 8.9 years (10 months-12 years) in our hospital were

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enrolled, in which 53 cases with viral infection and 32 cases with bacterial infection. Pathogenic diagnosis of all patients was confirmed via pathogen test or immunological examination.

Methods of determining PCT

Fasting venous blood was collected from children the next day after being admitted to hospital and 20 μl serum was got by centrifugation, then PCT in the serum was detected by semi-quantitative solid phase immunoassay.¹ PCT-Q test cards were made by B.R.A.H.M.S. Diagnostic Company in Berlin, Germany. The results were divided into four grades as $<0.5 \mu\text{g/L}$, $\geq 0.5 \mu\text{g/L}$, $\geq 2.0 \mu\text{g/L}$ and $\geq 10 \mu\text{g/L}$. The serum level of PCT $<0.1 \mu\text{g/L}$ was considered normal, PCT $\geq 0.5 \mu\text{g/L}$ were considered positive according to literature.

Statistical analysis

All children were divided into two groups according to viral infection and bacterial infection and the distribution of serum levels of PCT were compared.

Diagnostic sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy, positive likelihood ratio and negative likelihood ratio were calculated respectively according to the methods in literature. Statistical analysis was made by χ^2 test and Ridit analysis.

RESULTS

The distribution of serum levels of PCT

There were 53 cases with viral infection including mumps (23 cases), measles (7 cases), chickenpox (6 cases), Japanese encephalitis (5 cases), hepatitis A (4 cases), rubella (3 cases), hemorrhagic fever with renal syndrome (3 cases) and EB virus infection (2 cases). PCT levels of the majority of these viral infection patients were $<0.5 \mu\text{g/L}$. There were thirty two cases with bacterial infection including bacillary dysentery (8 cases), epidemic cerebrospinal meningitis (6 cases), bacterial pneumonia (4 cases), scarlet fever (4 cases), typhoid (3 cases), tuberculous meningitis (2 cases), urinary tract infection (2 cases) and tetanus (2 cases). PCT levels of the majority of these bacterial infection patients were $\geq 0.5 \mu\text{g/L}$ grade. The distribution of serum levels of PCT of all 85 cases was shown in Table 1.

Comparison on the distributions of serum levels of PCT between patients with virus infection and bacterial infection

PCT positive ratio of patients with bacterial infection was higher than that of patients with viral infection. Comparison on the distributions of serum levels of PCT between patients with virus infection and bacterial infection was shown in Table 2.

Relative parameters

According to the data in Table 2, if the serum level of $\text{PCT} \geq 0.5 \mu\text{g/L}$ was taken as positive threshold, the diagnostic sensitivity, specificity, positive predictive value, negative predictive value, the positive likelihood ratio, the negative likelihood ratio and the diagnostic accuracy of PCT for bacteria infection in the patients were 87.50%, 92.13%, 73.68%, 91.48%, 4.65, 0.15 and 83.53%, respectively.

DISCUSSION

For the patients with fever of unknown origin, peripheral leukocyte count and classification are often used to determine if there is bacterial infection and decide whether to use antibiotics or not. However, the result of peripheral leukocyte count and classification

Table 1. Distribution of serum levels of PCT of 85 cases

Disease	n	Serum level of PCT ($\mu\text{g/L}$)			
		<0.5	$\geq 0.5 - <2$	$\geq 2.0 - <10$	≥ 10
Viral infection					
Mumps	23	20	3	0	0
Measle	7	5	1	1	0
Chickenpox	6	5	1	0	0
Japanese encephalitis	5	3	1	1	0
Hepatitis A	4	3	1	0	0
Rubella	3	3	0	0	0
Hemorrhagic fever with renal syndrome	3	2	1	0	0
EB virus infection	2	2	0	0	0
Bacterial infection					
Bacillary dysentery	8	3	4	1	0
Epidemic cerebrospinal meningitis	6	0	1	3	2
Bacterial pneumonia	4	0	2	2	0
Scarlet fever	4	0	2	1	1
Typhoid	3	0	1	2	0
Tuberculous meningitis	3	0	2	1	0
Urinary tract infection	2	0	0	1	1
Tetanus	2	1	1	0	0
Total	85	47	21	13	4

Table 2. Comparison on the distributions of serum levels of PCT of viral infection and bacterial infection

Groups	n	Serum levels of PCT ($\mu\text{g/L}$)				Positive ratio (%)	$\bar{R} \pm S_{\bar{R}}$
		<0.5	$\geq 0.5 - <2.0$	$\geq 2.0 - <10$	≥ 10		
Viral infection	53	43	8	2	0	18.87	0.500 ± 0.040
Bacterial infection	32	4	13	11	4	87.50	0.141 ± 0.051
χ^2 or t value						$\chi^2=35.29$	$t=5.557$
P value						<0.001	<0.001

can be influenced by many factors, which result in obvious limitations for the sensitivity and specificity of diagnosis for bacterial infection. Currently, many foreign scholars have applied the serum level of PCT as an indicator of bacterial infection in a variety of clinical background (burns, organ transplants, ICU patients, children, etc.), the sensitivity and specificity were up to 55% and 80%, respectively, both were superior to peripheral leukocyte count and classification. Individual reports even indicated that the specificity of serum level of PCT reached 100%. Serum level of PCT can be used as an indicator for prognosis.^{2,3} Korppi et al studied on 132 cases of children with pneumonia and found that the percentage of serum PCT level $> 1 \mu\text{g/L}$ among children with *Streptococcus* pneumonia was 40%, while that among children with viral pneumonia was only 12% ($P < 0.05$). The cut-off limits of 0.5 ng/mL, 1.0 ng/mL and 2.0 ng/mL were tested for screening between *Streptococcus* pneumonia and viral pneumonia. The highest sensitivity of 55% was found at the 0.5 ng/mL cut-off level, whereas the highest specificity of 88% was reached at the level of 1.0 ng/mL.⁴ In the similar study, Nikfar et al found that the sensitivity and specificity of PCT were 77% and 89%, respectively, while in prediction of impaired renal function, C-reactive protein had a sensitivity of 80% and a specificity of 65%. They concluded that a rapid determination of PCT concentration could be useful for the management of children with febrile due to urinary tract infection in the emergency division.⁵

PCT is a kind of propeptide of calcitonin (CT) found in 1993. It is a glycoprotein composed of 116 amino acids without hormone activity, whose molecular weight is 13 kD and half-life is 25-30 h. It has good stability both in vitro and in vivo.² In physiological conditions, PCT may be produced by C cells in thyroid. The mRNA is translated into pre-PCT in the rough endoplasmic reticulum of C cells in thyroid. The pre-PCT is transferred into endoplasmic reticulum and forms PCT with 116 amino acid residues after glycosylation and removal of N-terminal signal peptide with specific enzyme, then with the help of different proteolytic enzymes, PCT is transformed into CT. In pathological conditions, PCT can be produced in liver, lung and other organs, peripheral monocytes also could produce PCT with the existence of lipopolysaccharide and some cytokine. Now PCT is considered as a kind of non-

steroidal anti-inflammatory substances and plays an important role in the regulation of cytokine network. All spliced products of propeptides of CT in the serum would increase in situation of severe bacterial infections or sepsis or other conditions, of which PCT is the most important product, while the CT does not change significantly. PCT can be detected just 2 h after the infection and reaches its peak level 12-18 h after the infection, falls back to normal in 2-3 days. In healthy individuals, circulating levels of procalcitonin are generally very low ($<0.05 \text{ ng/mL}$), so it can be regarded as abnormal when serum level of PCT was more than 0.5 ng/L. In the setting of severe bacterial infection and sepsis, the levels can increase by hundreds to thousands of folds within 4 to 6 hours.^{6,7} Procalcitonin level showed significant association with septic shock, positive blood culture and mental dysfunction.⁸

Our study showed that the distribution of serum levels of PCT of children with bacterial infection was obviously different from that of children with viral infection, and the differences between the two groups were significant ($P < 0.001$). If taking $0.5 \mu\text{g/L}$ as the threshold value of the serum level of PCT, the sensitivity of the diagnosis of bacterial infection was 87.50%, specificity was 92.13%, diagnostic accuracy was 83.53%, which was prior to the traditional peripheral leukocyte count and classification. In the study, it is believed that semi-quantitative detection of serum PCT is quick and easy to operate, and the serum level of PCT is a good indicator to differentiate bacterial infections and non-bacterial infection. During the clinical work, it's easy to make a preliminary diagnosis of whether there is bacterial infection or not, and decide whether to use antibiotics or not according to the serum level of PCT for the children with fever of unknown origin.

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