Research Article

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Serum neopterin and its significance as biomarker in differentiation of MODS from sepsis

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Abstract: Objective The aim of this study was to evaluate the dynamic changes of serum neopterin and its significance as biomarker in differentiation of MODS from sepsis.

Methods Fifty eight critical illness patients and 21 healthy controls were included in the study. Of the included 58 critical illness patients, 37 cases were diagnosed of sepsis (sepsis group) and other 21 were non-sepsis subjects (non-sepsis group). Of the 37 sepsis patients, 17 were diagnosed of multiple organ dysfunction syndrome (MODS group). The serum level of neopterin of the above subjects were examined by enzyme linked immunosorbent assay and compared between groups.

Results The serum level of neopterin were 0.885 ± 0.34 (ng/mL), 3.77 ± 2.08 (ng/mL), 14.80 ± 6.78 (ng/mL) and 23.90 ± 11.26 (ng/mL) for healthy control, non-sepsis, non-MODS and MODS groups respectively with significant statistical difference ($F=52.71$, $p<0.001$). Serum neopterin level of non-sepsis, non-MODS and MODS groups were statistical different in the time points of 0, 24h, 48h, 72h, and 96h ($p<0.05$). The serum neopterin level was significant higher in MODS group compared to non-sepsis and non-MODS groups ($p<0.05$). Using the serum neopterin as biomarker in differentiation of MODS from sepsis, the diagnostic sensitivity, specificity and AUC were 70.59% (95%CI:44.04-89.69) %, 80.00% (95%CI:56.34-94.27)% and 0.74(95%CI:0.57-0.91)% respectively.

Conclusion Serum neopterin levels in patients with sepsis were elevated and can be used as a promising biomarker in differentiation of MODS from sepsis.

Keywords: neopterin; sepsis; MODS; diagnosis; biomarker.

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Introduction

Sepsis is a serious systemic infectious disease with high incidence world-wide[1]. Clinical epidemiological study showed that 18 million new cases of sepsis occur annually in the world-wide, and 750 000 new cases occur annually in North America[2]. Moreover, the number of new cases of sepsis also increases at the rate of 1.5%-8.0% annually[3, 4]. Sepsis caused by bacteria, fungi, viruses, parasites and other pathogenic microorganisms is a common complication in patients with severe trauma, shock, infection and severe illness[5]. With the development of sepsis, it can develop into septic shock and multiple organ dysfunction syndrome (MODS) which is an important cause of death in critically ill patients.

Neopterin is a catabolic product of guanosine triphosphate (GTP). It belongs to the chemical group known as pteridines[6]. It is synthesised by human macrophages upon stimulation with the cytokine interferon-gamma(INF- γ) and is indicative of a pro-inflammatory immune status. Neopterin was an important biomarker of cellular immune system activation[7]. Neopterin is closely related to the pathological process of sepsis and other infectious complications[8]. In this study, we evaluate the dynamic changes of serum neopterin and its significance as biomarker in diagnosis of MODS in patients of sepsis neopterin.

Material and methods

Fifty eight critical illness patients in ICU and 21 healthy controls were recruited in the study. Of the 58 critical illness patients, 37 cases were diagnosed of sepsis and other 21 were non-sepsis subjects(non-sepsis). Of the 37 sepsis patients, 17 were diagnosed of multiple organ dysfunction syndrome (MODS). written informed consent was obtained in all the included subjects. The study was approved by the Medical Ethics Committee of Lishui People's Hospital, China. The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the

Table 1: General characteristics of the 3 groups[n(%)].

Characteristics	Sepsis(n=37)		Non-sepsis(n=21)
	MODS(n=17)	Non-MODS(n=20)	
Age			
≤50	7(41.2)	11(55.0)	11(52.4)
>50	10(58.8)	9(45.0)	10(47.6)
Gender			
Male	9(52.9%)	12(60.0%)	13(61.9%)
Female	8(47.1%)	8(40.0%)	8(38.1%)
Basic disease			
Craniocerebral trauma	3(17.6%)	2(10.0%)	1(4.8%)
Intracranial infection	1(5.9%)	1(5.0%)	1(4.8%)
Multiple injuries	3(17.6%)	2(10.0%)	3(14.3%)
Cerebral hemorrhage	1(5.9%)	1(5.0%)	0(0.0%)
Severe pulmonary infection	3(17.6%)	6(30.0%)	3(14.3%)
Pancreatitis	3(17.6%)	2(10.0%)	3(14.3%)
Intestinal obstruction	0(0.0%)	3(15.0%)	3(14.3%)
Purulent cholecystitis	3(17.6%)	2(10.0%)	2(9.5%)
Others	0(0.0%)	1(5.0%)	5(23.8%)

tenets of the Helsinki Declaration, and has been approved by the Lishui People's Hospital's institutional review board or equivalent committee. The general characteristics of the 58 critical illness patients was showed in **Table 1**. The 21 healthy controls were recruited from people who came to our hospital for routine physical examination. There were 10 male and 11 female subjects in the healthy control group with the mean age of 48.36 ± 11.22 . The sepsis and MODS diagnosis were showed in **Supply table 1**.

Serum neopterin measurement in serum

Within 24 hours after patients admission, 5mL of peripheral venous blood was taken from each patient. The blood was separated and stored in a refrigerator at -20°C for next usage. The serum level of neopterin was examined by enzyme linked immunosorbent assay.

Statistical analysis

The measurement data were expressed by mean values and standard deviations and the comparison of the groups was analyzed by variance analysis and student-t test was used for each two groups comparison. The sensitivity, specificity, and the area under the ROC curve were calculated by the

equation of sensitivity=true positive/(true positive+ false negative), specificity=true negative/(true negative+ false positive). Two tails $p < 0.05$ meant a statistical difference. The statistical analysis was performed by SPSS17.0 software (SPSS, Inc., Chicago, IL, USA). The graph was drawn by Graphpad Prism 7.0 software (<http://www.graphpad.com/scientific-software/prism/>).

Results

1 serum neopterin concentration at the time of admission

The neopterin serum level of healthy control, non-sepsis, non-MODS and MODS groups were showed in **Figure 1**. The serum level of neopterin were $0.885 \pm 0.34(\text{ng/mL})$, $3.77 \pm 2.08(\text{ng/mL})$, $14.80 \pm 6.78(\text{ng/mL})$ and $23.90 \pm 11.26(\text{ng/mL})$ for healthy control, non-sepsis, non-MODS and MODS groups respectively with significant statistical difference ($F=52.71$, $p < 0.001$)

2 Dynamic changes of serum neopterin

Serum neopterin level of non-sepsis, non-MODS and MODS groups were statistical different in different time

Figure 1: Serum neopterin concentration at the time of admission for different groups.

points ($p<0.05$), **Figure 2**. The serum neopterin level was significantly higher in MODS group compared to non-sepsis and non-MODS group ($p<0.05$), **Table 2**.

3 Diagnostic performance of serum neopterin as biomarker for MODS

Using the serum neopterin as biomarker in differentiation of MODS from sepsis, the diagnostic sensitivity, specificity and AUC were 70.59% (95%CI:44.04-89.69%), 80.00%(95%CI:56.34-94.27)% and 0.74(95%CI:0.57-0.91) respectively, **Figure 3**.

Table 2: Serum neopterin concentration of different time points in different groups(ng/mL).

Time point	Non-sepsis	Non-MODS	MODS
0	3.77±2.08	14.80±6.78	23.90±11.26
24	4.21±2.21	16.23±7.14	24.56±10.23
48	3.86±1.98	18.21±8.12	25.12±12.45
72	3.85±2.02	19.50±8.56	23.21±14.12
96	4.02±2.11	17.24±7.56	22.14±11.23

Figure 2: Dynamic changes of serum neopterin level in patients of different groups.

Figure 3: The ROC curve for serum neopterin in differentiation of MODS from sepsis.

Discussion

Epidemiology study demonstrated that the incidence of sepsis was 15.7% in critically illness patients, and of which 61.1% will further develop MODS with the mortality of 30.6%[9]. Therefore, early diagnosis of sepsis, MODS and early effective intervention is of great significance in patients with critical illness. At present, sepsis, septic shock and MODS are considered to be a dynamic process reflecting a series of pathophysiological changes. The essence of the process is that the systemic inflammatory response is constantly aggravated and deteriorated, and the balance between the compensatory anti-inflammatory response and sepsis is destroyed.

Neopterin is a low molecular weight pyridine derived from the metabolism of guanosine triphosphate (GTP). Although the exact role of neopterin in the process of immune and inflammatory responses has not been fully elucidated yet. Recent studies have revealed that neopterin was an important biomarker of the degree of cellular immune activation mediated by the lymphocyte-macrophage axis in vivo[10, 11]. In vivo and in vitro experiments have confirmed that cellular immune response was accompanied by increased production of neopterin[12, 13]. Detection of neopterin levels in body fluids (such as serum, urine, etc.) was helpful to reflect the cellular immune status in a variety of diseases[11, 14].

High neopterin level is associated with increased production of reactive oxygen species, neopterin concentrations also allow to estimate the extent of oxidative stress elicited by the immune system[13, 15, 16]. Measurement of neopterin concentrations in body fluids such as serum, cerebrospinal fluid or urine can provide useful information of disease severity or treatment response[17]. Pacher et al[18] examined the neopterin level of 56 critically ill patients in ICU. Among them, 32 patients with sepsis and MODS had significantly elevated levels of neopterin. The levels of neopterin in blood were positively correlated with the score of MODS (according to Go RIS score). The sensitivity and specificity of neopterin as biomarker in diagnosis of MODS were 96% and 73% respectively with the cut off value of > 40 nmol/L.

In our present study, we included 17 MODS, 20 non-MODS sepsis patients and compared the serum concentration between the two groups. We found that

the serum neopterin in MODS patients were significant elevated compared to non-MODS sepsis cases. And using the serum neopterin as serological marker, the diagnosis sensitivity and specificity were relative high. This diagnostic efficacy was not as good as Pacher's results[18]. This may because of the small sample size in MODS which lead to limited statistical power in our study.

In conclusion, our study found that serum neopterin levels in patients with sepsis were elevated and can be used as a promising biomarker for differentiation of MODS from sepsis. And dynamic measurements of serum neopterin level maybe helpful in early diagnosis of MODS, which may provide useful information for MODS treatment and then improve the patient's prognosis.

Conflict of interest: None

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