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Original Article

Serum antioxidant status of bilirubin, albumin, uric acid, and creatinine in patients with meningitis

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Abstract: Objective: Oxidative stress, closely related to inflammation, plays an important role in the pathophysiology of central nervous system infections. Low levels of antioxidant indicators, including albumin and uric acid (UA), in meningitis have been reported in previous studies. However, there are no studies comprehensively clarifying the changes of common serum endogenous antioxidants in meningitis and comparing them in different types of meningitis, such as bacterial meningitis (BM), tuberculous meningitis (TM), and viral meningitis (VM). Methods: The current study aimed to explore changes in common serum endogenous antioxidants in different types of meningitis. This study collected clinical characteristics and serum total bilirubin (Tbil), albumin, UA, and creatinine levels in 220 common meningitis patients and 238 healthy controls (HC). The collected information was analyzed. Results: It was found that serum albumin, UA, and creatinine levels were lower in meningitis patients than in HC. Moreover, serum albumin and UA were the lowest in BM, followed by TM and VM. There were no significant changes in serum Tbil levels. Furthermore, women showed lower serum endogenous antioxidants levels than men, both in meningitis and HC groups. Multivariate logistic analysis showed that albumin, UA, and creatinine were relevant factors for meningitis after separately adjusting for age and gender. Conclusion: Patients with meningitis have low levels of serum albumin, UA, and creatinine, indicating low serum antioxidant states in meningitis. Moreover, serum albumin and UA tend to be lower in BM, followed by TM and VM. Changes in serum Tbil, however, remain uncertain.

Keywords: Meningitis, antioxidant, albumin, uric acid, creatinine

Introduction

Meningitis, the most common form of central nervous system (CNS) infections, seriously influences lives and health due to high morbidity, mortality, and disability. Common pathogens of meningitis include bacteria, viruses, tuberculous mycobacteria, and fungi [1]. Inflammation may be one of the main causes of pathological damage in meningitis, but the pathological process is far more complex [2, 3]. Studies have indicated that oxidative stress injuries, closely related to inflammatory reactions, play an important role in the pathogenesis of meningitis [4, 5]. Large amounts of reactive oxygen species (ROS), reactive nitrogen species (RNS), and peroxynitrite were found to be produced in patients with pneumococcal meningitis. These substances exert a variety of toxic actions, including lipid peroxidation, poly-ADP-ribose polymerase (PARP) activation after DNA strand breakage and subsequent cellular energy consumption, activation of matrix metalloproteinases, and production of inflammatory cytokines [4]. Excessive ROS irreversibly damages the structure and function of cells [6]. Interactions caused by these substances lead to disruption of blood-brain barriers, massive meningeal inflammation, brain edema formation, and neuronal necrosis [7-9]. Therefore, decreased ability to resist oxidative stress may also be involved in pathologic damage caused by meningitis.

Many previous studies have shown that serum antioxidant levels were lower in patients with meningitis than in healthy controls, with a decrease of serum albumin and uric acid (UA) reported. [10-13]. In addition, other oxidative and antioxidative related indicators, including serum bilirubin, acrolein-lysine, and nitrite, ha-

Table 1. Demographic and clinical characteristics of patients with meningitis and healthy controls

Characteristics	Meningitis (n=220)	BM (n=61)	TM (n=65)	VM (n=94)	HC (n=238)
Age (years)*	32.5 (24.5, 50.75)	40 (26.5, 57.5)	45 (31, 59)	27 (20, 34)	50 (38, 58)
Gender, male, n (%)	124 (56.36%)	32 (52.46%)	37 (56.92%)	55 (58.51%)	136 (57.4%)
History of head injury and surgery, n (%)	27 (12.27%)	20 (32.79%)	3 (4.62%)	4 (4.25%)	
Symptoms					
Fever, n (%)	214 (97.27%)	61 (100%)	64 (98.46%)	89 (94.68%)	
Headache, n (%)	200 (90.91%)	52 (85.25%)	60 (92.31%)	88 (93.62%)	
Vomit, n (%)	109 (49.55%)	33 (54.09%)	26 (40%)	50 (53.19%)	
Seizure, n (%)	5 (2.27%)	4 (6.56%)	0 (0%)	1 (1.06%)	
Conscious disturbance	41 (18.64%)	25 (40.98%)	13 (20%)	3 (3.19%)	
CSF					
WBC count (/uL)*	206.5 (87.75, 600.75)	1850 (740, 4760)	200 (135, 370)	92 (42, 214)	
Protein (mg/L)*	1214 (574, 2818)	2981 (1291, 6433)	2248 (1410, 2970)	546 (374, 808)	
Glucose (mmol/L)*	2.7 (1.7, 3.2)	1.6 (<1.1, 2.8)	2.1 (1.4, 2.6)	3.1 (2.8, 3.5)	
Chloride (mmol/L)*	117 (113, 120)	115 (113, 118)	112 (106, 117)	119 (117, 121)	
Blood leukocyte count (×10^9/L)*	8.23 (6.08, 11.5)	13.5 (9.05, 23.05)	7.8 (5.85, 10.24)	6.99 (5.5, 9.77)	
Poor outcome, n (%)	13 (5.91%)	6 (9.84%)	5 (7.69%)	2 (2.13%)	

CSF: cerebrospinal fluid; BM: bacterial meningitis; TM: tuberculous meningitis; VM: viral meningitis; HC: healthy controls; Poor outcome: patients were unconscious or dead at discharge. *: Data is presented by median (first quartile, third quartile).

ve been reported to be associated with meningitis [11, 14].

Bilirubin has long been considered as the cytotoxic metabolite of iron porphyrin. However, it now has been reported to have other important functions, such as anti-inflammatory, antioxidant, cytoprotective, and neuroprotective activities, along with immunomodulatory effects [15, 16]. It has stronger antioxidant capacity than α-tocopherol (Vit E), catalase, and superoxide dismutase [15, 17]. Serum albumin decreases rapidly under conditions of trauma, infection, and malignant tumors. This may be related to reduced synthesis, increased consumption, and redistribution [18-20]. It was also claimed as a major known antioxidant, accounting for half of the total antioxidant capacity of serum, taking effect through ligand and free radical trapping [21]. In addition, UA, an important outcome of purine metabolism and possessing metal-chelating properties, is a major antioxidant [22]. Furthermore, UA has presented therapeutic effects on meningitis in animal experiments [23]. Creatinine has also been demonstrated as a kind of serum endogenous antioxidant factor [24].

Previous studies have not comprehensively clarified changes in these common serum endogenous antioxidants in meningitis or compared them in different types of meningitis, such as bacterial meningitis (BM), tuberculous meningitis (TM), and viral meningitis (VM). Therefore, the present hospital-based cross-sectional study was conducted to compare these serum antioxidant levels (serum total bilirubin (Tbil), albumin, UA, and creatinine) of meningitis patients with healthy controls (HC). Moreover, these indicators were compared among three different types of meningitis. This study was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University.

Materials and methods

Clinical data collection and definitions

This study reviewed the patient record system and gathered the information of adult meningitis patients (aged 16 or older), admitted to the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China, from January 2006 to March 2016. This study involved 458 individuals, including 220 meningitis patients (61 BM patients, 65 TM patients, and 94 VM patients) and 238 healthy controls. Diagnosis of TM referred to Vietnam diagnostic criterion [25]. Diagnosis of BM and VM referred to another relevant study [26]. Relevant data were collected, including clinical symptoms and signs, cerebrospinal fluid (CSF) characteristics, some blood indexes, imaging manifestations, and prognosis.

Exclusion criteria were: Subjects with liver disease, abnormal liver function (abnormal ranges of alanine transaminase (ALT) and aspartate transaminase (AST) concentration), diabe-

Table 2. Serum Tbil, albumin, UA, and creatinine levels in meningitis patients and healthy controls

	Meningitis patients			Healthy controls			P^1	P^2	P^3	P^4	P^5
	Total	Male	Female	Total	Male	Female					
Tbil (umol/L)*	11 (8, 17)	12 (10, 17)	9 (7, 16.5)	12 (10, 16)	12.5 (9.25, 16.75)	12 (10, 15)	0.13	0.831	0.006	0.001	0.402
Albumin (g/L)#	40.14±5.04	40.89±5.30	39.18±4.53	46.62±3.05	47.66±2.83	45.23±2.79	<0.001	<0.001	<0.001	0.02	<0.001
UA (umol/L)#	211.55±87.94	244.23±90.89	169.35±62.75	348.16±82.63	386.97±68.78	296.42±70.47	<0.001	<0.001	<0.001	<0.001	<0.001
Creatinine (umol/L)#	58.29±14.48	64.81±12.61	49.85±12.24	65.61±12.96	73.31±9.92	55.33±8.71	<0.001	<0.001	0.003	<0.001	<0.001

Tbil: total bilirubin; UA: uric acid. *: Data is presented by median (first quartile, third quartile); #: data is presented by mean ± standard deviation; P^1: patients with meningitis vs. healthy controls; P^2: male patients with meningitis vs. male healthy controls; P^3: female patients with meningitis vs. female healthy controls; P^4: male vs. female in meningitis group; P^5: male vs. female in healthy controls.

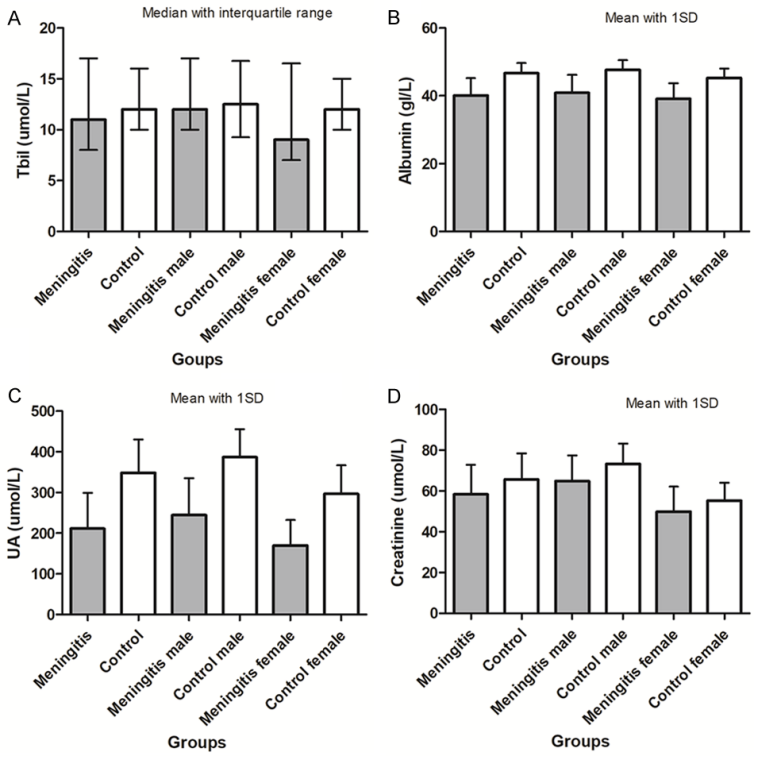

Figure 1. Serum Tbil, albumin, UA, and creatinine levels in meningitis patents and healthy controls. Tbil: total bilirubin; UA: uric acid.

tes, and renal dysfunction, as well as those that had used steroids before [27]. In addition, the following subjects were excluded: 1) Individuals receiving other drugs that would affect serum Tbil, albumin, UA, and creatinine levels; 2) Individuals with cancer and gout; and 3) Individuals without a definitive diagnosis. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Research Committee and with the 1964 helsinki declaration and its later amendments or comparable ethical standards.

Laboratory assessment of serum bilirubin, albumin, UA, and creatinine

Fasting venous blood of all subjects was monitored after hospitalization. Concentrations of serum Tbil, albumin, UA, and creatinine were detected by a Clinical Analyzer Beckman Coulter AU5800 (Beckman Coulter, California, American). Serum alanine transaminase (ALT) (normal range: 9-50 μmol/L for males, 7-40 μmol/L for females) and aspartate transaminase (AST) (normal range: 15-40 μmol/L, 13-35 μmol/L for females) concentrations were detected as well.

Statistical analysis

Data analyses were performed using Statistical Program for Social Sciences (SPSS) software (version 19.0, SPSS Inc, Chicago, IL, USA). Measurement data accorded with normal distribution (albumin, UA, and creatinine) are presented as mean ± standard deviation (SD). Measurement data accorded with non-normal distributions (e.g., Tbil, age, CSF indexes) are presented as medians (first quartile, third quartile). Enumeration data (symptoms, gender, and prognosis) are presented by rates. Comparisons of serum antioxidants levels (serum albumin, UA, and creatinine) between patients with meningitis and controls were performed by covariance analysis, with age as covariant. Covariance analysis was also used to compare serum antioxidants levels between subgroups, classified according to genders, with age as the covariant. One-way analysis of variance (ANOVA) and least significant difference t-tests (LSD-t) were used to test distinctions of serum albumin, UA, and creatinine among three types of meningitis and controls. Mann-Whitney U-tests and Kruskal-Wallis tests were used to compare serum Tbil among meningitis patients and controls. Logistic regression analysis was performed to determine factors related with meningitis. Age and gender were adjusted for each antioxidant indicator. *P*-values less than 0.05 indicate statistical significance.

Results

Clinical characteristics of subjects

This research included 238 healthy individuals and 220 meningitis patients [61 BM (male 32, female 29), 65 TM (male 37, female 28) and 94 VM (male 55, female 39)]. There were no significant differences in gender among HC and

Table 3. Serum antioxidants among healthy controls and three types of meningitis

Variables	BM	TM	VM	HC	P
Tbil (umol/L)*	11 (8, 9)	12 (9, 18)	10 (8, 15)	12 (10, 16)	0.08
Albumin (g/L)#	37.84±5.49[a,b,c]	40.64±5.43[a]	41.29±3.9[a]	46.62±3.05	<0.001
UA (umol/L)#	179.98±81.16[a,b,c]	215.94±93.10[a]	229.01±83.79[a]	348.16±82.63	<0.001
Creatinine (umol/L)#	58.44±13.76[a]	55.68±15.28[a]	59.99±14.25[a]	65.61±12.96	<0.001

Tbil: total bilirubin; UA: uric acid; BM: bacterial meningitis; TM: tuberculous meningitis; VM: viral meningitis; HC: healthy controls. *: Data is presented by median (first quartile, third quartile); #: data is presented by mean ± standard deviation; a: P<0.05 with respect to healthy controls; b: P<0.05 with respect to viral meningitis; c: P<0.05 with respect to tuberculous meningitis.

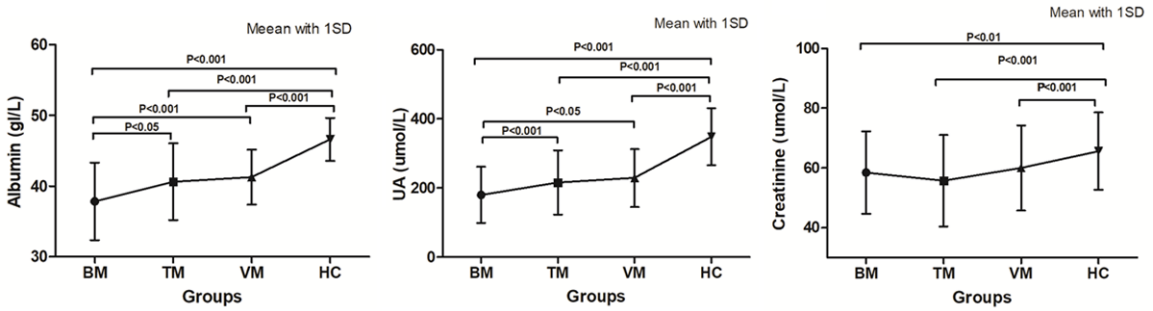

Figure 2. Serum albumin, UA, and creatinine among healthy controls and three types of meningitis. UA: uric acid; BM: bacterial meningitis; TM: tuberculous meningitis; VM: viral meningitis; HC: healthy controls.

the three groups of meningitis (p=0.899). Demographic and clinical characteristics of patients and HC are shown in **Table 1**. Patients that were unconscious or dead at discharge were defined as poor outcomes.

Comparison of serum antioxidants between meningitis and healthy subjects adjusted for age and gender

In this study, there were no statistically significant differences between meningitis patients and HC in serum Tbil, while adjusting for age (P=0.13) (**Table 2**, **Figure 1A**). Levels of serum albumin, UA, and creatinine in the meningitis group were significantly lower than those in the healthy group after adjusting for age all P< 0.001) (**Table 2**, **Figure 1B-D**). Groups were further divided into four subgroups according to genders, further eliminating the effects of genders (**Table 2**, **Figure 1**). There were no significant differences comparing the serum Tbil of male meningitis patients to male healthy individuals (P=0.831). In female groups, however, serum Tbil in meningitis was significantly lower than in controls (P=0.006). Furthermore, it was found that other serum anti-oxidative indexes (albumin, UA, and creatinine) in male patients with meningitis were significantly lower than male HC (all P<0.001). The same results were discovered when comparing female subgroups (female meningitis patients vs. female controls; all P<0.01). Regarding gender discrepancies, almost all of serum antioxidants were significantly lower in females than males (both in meningitis group and healthy group), except the comparison of serum Tbil between healthy men and healthy women (P=0.402).

Comparison of serum antioxidants among HC and three types of meningitis

Differences in serum endogenous antioxidants levels among different meningitis and HC are presented in **Table 3** and **Figure 2**. Subgroups were not divided further according to genders, as gender composition among normal subjects and three types of meningitis patients showed no statistical discrepancies (p=0.899) and the size of the sample was not large enough. Serum Tbil showed no significant differences among subgroups of meningitis and HC (P=0.08). Mean concentrations of serum albumin and UA were the lowest in BM (albumin 37.84±5.49 g/L, UA 179.98±81.16 umol/L), the second lowest in TM (albumin 40.64±5.43 g/L, UA 215.94±93.10 umol/L), the third lowest in VM (41.29±3.9 g/L, UA 229.01±83.79

umol/L, and the highest in HC (albumin 46.62± 3.05 g/L, UA 348.16±82.63 umol/L). Furthermore, significant differences of serum albumin and UA were found in almost all comparisons between any two groups mentioned above, except the comparison between TM and VM (albumin: P=0.319, UA: P=0.317). Serum creatinine concentrations were 58.44±13.76 umol/L in BM, 55.68±15.28 umol/L in TM, and 59.99±14.25 umol/L in VM. No differences existed among the comparisons (BM vs. TM, P=0.257; BM vs. VM, P=0.492; TM vs. VM, P= 0.051), but serum creatinine in all subgroups of meningitis was significantly lower than the HC group (65.61±12.96 umol/L).

Logistic regression for antioxidants in meningitis compared with healthy controls

Logistic regression analysis was conducted to calculate odd ratios of Tbil, albumin, UA, and creatinine for meningitis, as presented in **Table 4**. After adjusting for age and gender for each anti-oxidative indicator, multivariate logistic regression suggests that serum albumin, UA, and creatinine were relevant factors for meningitis (albumin, OR 0.561, 95% CI [0.502, 0.626], P<0.001; UA, OR 0.975, 95% CI [0.971, 0.980], P<0.001; creatinine, OR 0.942, 95% CI [0.923, 0.961], P<0.001) (**Table 4**). However, serum Tbil was not a relevant factor for meningitis after adjusting for age and gender (OR 1.007, 95% CI [0.978, 1.038], P=0.623) (**Table 4**).

Discussion

Under physiological conditions, antioxidants are competent in avoiding ROS damage to the host. An imbalance of oxidation and anti-oxidation systems, in other words, a bias towards oxidation, would irreversibly damage cellular metabolism and cell structures, including membrane lipids, proteins, carbohydrates, and DNAs [6, 28]. Changes in serum antioxidants have been proven to be involved in many CNS diseases, such as multiple sclerosis, myasthenia gravis, ischemic strokes, and CNS infections [10, 11]. Research has shown that oxidative stress injuries, combined with inflammation, play an important role in the pathological process of meningitis, aggravating the brain edema formation, blood-brain barrier damage, and neuronal necrosis [7-9]. Some studies have applied antioxidants (phenylbutyl nitro, n-acetylcysteine) into the treatment for meningitis in rat models. They hypothesized that these antioxidants may be able to weaken meningeal inflammation and improve intracranial hypertension, blood-brain barrier destruction, and vascular dysfunction [8, 9].

Serum albumin, Tbil, UA, and creatinine are common endogenous antioxidants. Serum albumin decreases rapidly under conditions of trauma, infection, and malignant tumors [18]. It takes up the majority of total antioxidative capacity and it is inversely related to inflammatory levels. Decreased serum albumin levels reflect the status of inflammation and decreased antioxidant capacity [29]. In addition, albumin may act as an antioxidant to defend oxidative stress when under pathologic conditions, such as inflammation. It may directly scavenge hydroxyl radicals and HOCL and other free radicals [21, 30]. In the current study, serum albumin levels were decreased in patients with meningitis, in which the BM group had the lowest levels. Hypoalbuminemia is more severe in patients with BM. This may be related to its more severe inflammatory response. Serum albumin is an important antioxidant substance. Present results reflect the decreased ability of patients with meningitis to resist oxidative stress, especially in BM, followed by TM, then VM. Another indicator that has been widely studied is UA. It was affirmed that peroxynitrite (ONOO-) is produced largely under oxidative stress and that it enhances blood-brain barrier (BBB) penetrability, promoting cell invasion in the CNS. UA, as the scavenger of ONOO-, could lessen damage of blood brain barrier and inflammation [31, 32]. In this study, serum UA decreased significantly in patient with meningitis, especially those with BM. Similar results have been presented in other studies [10-12]. Creatinine has been demonstrated as a potential serum endogenous antioxidant that may guard against oxidant oxidative lesions in myasthenia gravis [24, 33]. In the present study, creatinine was lower in patients with meningitis, but no statistical differences existed among different types of meningitis. Further studies are necessary to clarify whether creatinine is a certain serum endogenous antioxidant and to clarify its role in intracranial infections. Bilirubin, an endogenous product of heme metabolism, is a prominent antioxidant cytoprotector. It takes effect mainly through protecting lipids from oxidative stress damage [34]. In a previous study on the total antioxidant/oxidant sta-

Table 4. Logistic regression model* with risk factors of meningitis compared with healthy control

Variables	Adjusted OR (95% CI)	P
Tbil (umol/L)	1.007 (0.978, 1.038)	0.623
Albumin (g/L)	0.561 (0.502, 0.626)	<0.001
UA (umol/L)	0.975 (0.971, 0.980)	<0.001
Creatinine (umol/L)	0.942 (0.923, 0.961)	<0.001

Tbil: total bilirubin; UA: uric acid. *: Age and male are adjusted for each variable above.

tus in meningism and meningitis, levels of serum Tbil were not significantly different among meningismus, meningitis, and controls [13]. Similarly, present research showed no differences in Tbil levels between meningitis and HC and no significant differences among different types of meningitis. However, according to subgroup analysis, serum Tbil levels were lower in the female meningitis group than the female control group, but no statistical differences were found in males. In contrast, a few previous studies described an increase of serum Tbil in meningitis patients, suggesting raised serum bilirubin as a defense strategy against oxidative stress [11, 14]. These inconsistent outcomes may be caused by the following reasons: 1) Patients with abnormal liver function had not been excluded in their studies; and 2) Sample sizes of these studies was too small. Changes in serum Tbil levels and their effects on meningitis require further examination.

Serum albumin, UA, and creatinine were significantly decreased in patients with meningitis. Moreover, serum albumin and UA were the lowest in BM, followed by TM, then VM. Results suggest that the serum antioxidant capacity of meningitis patients is decreased and the degree of reduction varies among different types of meningitis. This reduction in antioxidant capacity may be related to the extent of the inflammation, which leads to consumption of these antioxidants during the scavenging of excessive free radicals [35]. Raising levels of serum endogenous antioxidants may be a new therapeutic option for meningitis.

Furthermore, the current study showed that almost all serum antioxidants levels (Tbil, albumin, UA, and creatinine) in men were higher than in women, both in meningitis and healthy subjects. This result is consistent with previous findings [33]. Results suggest a lower state of oxidative stress and anti-oxidative defense existing in females than in males. Previous studies have considered that estrogen might play a part in regulation of oxidative stress, resulting in the low state of oxidative stress in females [36].

This study systematically and comprehensively analyzed serum antioxidative statuses of Tbil, albumin, UA, and creatinine in meningitis, comparing them in different types of meningitis. This study had the following limitations, however: 1) Indicators stated above had not been obtained at the recovery phase of diseases and analyzed further; 2) The sample size in this research was not large enough.

Conclusion

Present finding suggested that patients with meningitis have low levels of serum albumin, UA, and creatinine, indicating the low serum antioxidant status in meningitis. Moreover, serum albumin and UA tended to be lower in BM, followed by TM, then VM. Results suggest that those serum antioxidant levels reflect the degree of inflammation and antioxidant capacity of different types of meningitis. Maybe the inflammation occurring in meningitis and the scavenging for excessive free radicals leads to reduction in serum levels. The mechanisms and effects of serum antioxidants in meningitis are complicated and require further research.

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Disclosure of conflict of interest

None.

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