

Clinical characteristics and cerebro-spinal fluid cytokine changes in patients with acquired immunodeficiency syndrome and central nervous system infection

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Abstract. Clinical characteristics and the cerebro-spinal fluid (CSF) cytokine changes in acquired immunodeficiency syndrome (AIDS) patients with tuberculous meningitis and cryptococcal meningitis in central nervous system (CNS) infections before and after treatment were investigated. The clinical records of 80 AIDS patients with CNS infections and 40 non-CNS infection patients hospitalized in the Infection Department of the First Hospital of Changsha from February 2013 to March 2016 were retrospectively analyzed. Forty-one cases of AIDS complicated with tuberculous meningitis were enrolled as group A, 39 cases of AIDS complicated with cryptococcal meningitis as group B, and 40 cases of non-CNS infection with lumbar puncture indication as group C. The general data, clinical symptoms, CSF examination and prognosis of the three groups of patients were collected. Of the 80 patients, 56 patients were discharged from hospital (improvement group) and 24 died (death group) after treatment. The concentrations of interferon- γ (IFN- γ), interleukin-6 (IL-6), interleukin-10 (IL-10) and tumor necrosis factor- α (TNF- α) in CSF were detected by enzyme-linked immunosorbent assay. There were significant differences in clinical manifestations, CSF pressure, CSF leucocyte count, CSF glucose, CSF chloride and CSF protein between group A, group B and group C ($P<0.05$). The concentrations of IFN- γ , IL-6, IL-10 and TNF- α in CSF of group A and group B increased significantly compared with group C ($P<0.001$). The IL-6, IL-10 and TNF- α levels in CSF in the improvement group were significantly lower than those in the death group ($P<0.001$), while the concentration of IFN- γ increased significantly ($P<0.001$). CSF biochemistry

is characterized by increased pressure, leucocyte count and protein, and decreased chloride and glucose. IFN- γ , IL-6, IL-10 and TNF- α in CSF have certain predictive value for poor prognosis of AIDS patients with CNS infection.

Introduction

Acquired immunodeficiency syndrome (AIDS) is a serious immunodeficiency disease infected by human immunodeficiency virus (HIV) (1). AIDS patients are mostly promiscuous, multi-transfused, homosexual and intravenous drug addicted. Sexual transmission is the main route of the transmission of HIV infection, while other routes are mother-to-child transmission, blood product transfusion, organ transplantation and drug use with syringes (2). At present, the number of AIDS patients worldwide has reached 37 million, and the incidence has increased year by year (3). AIDS is mainly manifested by fatigue, fever and other clinical symptoms, with the characteristics of slow onset and high fatality rate. It mainly invades the immune system of patients, causing serious damage to their immune function (4). AIDS can gradually develop into a secondary infection, prone to various pathogenic bacteria infections. In clinical practice, central nervous system (CNS) infections are common in AIDS patients (5).

The CNS of the normal human body can resist the invasion of various pathogens, but AIDS patients have impaired immune function and decreased resistance, and the brain and spinal cord are easily infected by various pathogens, which in turn leads to CNS infection (6,7). Opportunistic CNS infection is the most common complication in patients with advanced AIDS (8). CNS infections are usually encephalitis caused by bacteria invading the CNS and meningitis caused by spinal pachymeningitis or meninges. The most common CNS infection diseases in AIDS patients are tuberculous meningitis and cryptococcal meningitis (9,10). Tuberculous meningitis is a non-suppurative inflammation of CNS, mostly caused by the invasion of tubercle bacillus of the ependyma and meninge into subarachnoid space. Cryptococcal meningitis is a chronic inflammatory disease with chronic or subacute infection of CNS infected by *Cryptococcus neoformans*. AIDS complicated with tuberculous meningitis or cryptococcal meningitis is the main cause of death (11,12). There

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is a close relationship between the human immune system and the nervous system, and when CNS infection occurs, the levels of various cytokines in the body will be abnormally expressed (13).

At present, there is no report on the clinical characteristics and cerebro-spinal fluid (CSF) cytokines changes in AIDS patients with tuberculous meningitis and cryptococcal meningitis. The aim of this study was to provide a feasible method for the early diagnosis and prognosis of AIDS patients with CNS infectious diseases by observing the clinical symptoms of AIDS patients with tuberculosis meningitis and cryptococcal meningitis and the significance of cytokines in CSF.

Materials and methods

General data. The clinical records of 80 AIDS patients with CNS infection and 40 non-CNS infection patients hospitalized in the Infection Department of The First Hospital of Changsha (Changsha, China) from February 2013 to March 2016 were retrospectively analyzed. Forty-one AIDS patients complicated with tuberculous meningitis were enrolled as group A, including 29 males and 12 females, with an age range of 23-67 years and an average age of 36.15 ± 10.63 years; 39 AIDS patients complicated with cryptococcal meningitis were enrolled as group B, including 27 males and 12 females, with an age range of 20-72 years and an average age of 34.14 ± 11.42 years; and 40 patients with non-CNS infection with lumbar puncture indication were enrolled as group C, including 25 males and 15 females, with an age range of 25-67 years and an average age of 33.09 ± 9.15 years.

This study was approved by the Ethics Committee of The First Hospital of Changsha. All the subjects were informed and agreed to participate in the clinical study, and signed a complete informed consent form.

Inclusion and exclusion criteria. Inclusion criteria were: in line with the AIDS diagnostic criteria of the US Centers for Disease Control and Prevention (CDC) 2015 (14), enzyme linked immunosorbent assay (ELISA) and western blot confirmed HIV antibody as positive; the clinical symptoms were headache, fever, nausea, consciousness disorder and meningeal irritation; tuberculous meningitis patients with acute and subacute clinical symptoms, and mycobacterium tuberculosis detected by CSF smear; patients diagnosed with cryptococcal meningitis by fungal ink staining, fungal culture, urease test and imaging examination; patients receiving no anti-tuberculosis, anti-cryptococcus neoformans and highly active anti-retroviral therapy (HAART) in the past. Exclusion criteria were: patients complicated with deep fungal infections such as candidiasis, histoplasmosis and penicilliosis marneffeii; patients with severe liver, kidney and hematopoietic dysfunction; patients with mental illness or a family history of mental illness.

Research methods. The general data, clinical symptoms, CSF examination and prognosis of 3 groups of patients were collected. The CSF biochemical indexes (including pressure, leucocyte count, glucose, chloride, protein) were detected within 1 day after admission, and the death of patients during admission was recorded. The clinical data, treatment and

prognosis of the patients, as well as the follow-up results were summarized.

Treatment outcome. Patients in group A were given anti-tuberculosis treatment with 2 HRZE/4HR regimen. Whereas patients in group B were treated with 1,200 mg/day oral fluconazole for 15 days, followed by 400 mg/day for 45 days and 200 mg/day for life. Patients in the two groups received HAART at the 3rd week of treatment. If the patients were able to tolerate anti-infection and anti-retroviral treatment, HAART was continued. If not, HAART was terminated and other symptomatic treatment was given. Judgment criteria for improvement: no meningeal irritation sign, local orientational sign of nervous system and consciousness disorder. Of the 80 patients, 56 improved and were discharged, and 24 died after treatment, with a fatality rate of 30.00%. The 56 patients who improved were considered as the improvement group and the 24 patients who died as the death group.

Sample collection and detection. CSF (5 ml) from the lower lumbar spine of three groups of patients was extracted using spinal cord puncture method and centrifuged (Hunan Hengnuo Instrument Equipment Co., Ltd., Changsha, China) at $1,500 \times g$, 4°C for 10 min, and the separated supernatant was stored in a refrigerator at -20°C (Shanghai Coolingway Biotechnology Co., Ltd., Shanghai, China) for later use. The concentrations of IFN- γ , IL-6, IL-10 and TNF- α in CSF were detected by ELISA with reference to the instructions of human IFN- γ , IL-6, IL-10 and TNF- α ELISA kits [Abcam (Shanghai) Trading Co., Ltd., Shanghai, China]. For the detection method the sample well, standard well, negative control group and positive control group were set up. Standard solution (100 μl), test sample, negative and positive control solution were absorbed into the reaction wells, and 100 μl of the biological reaction antibody solution was added quickly, covered with a film, mixed well and kept for 40 min. Then, 100 μl of streptavidin was added to each reaction well, covered with a film, mixed evenly and then left to stand for 40 min. The liquid in the reaction wells was poured out, and the washing liquid was added to each well, shaken slightly for 1 min, then discarded. The process was repeated five times. Substrate of reaction solution A (100 μl) and reaction solution B was added into each reaction well, covered with film, and kept in the dark for 5 min. Subsequently, 100 μl of elimination agent was added into wells and then the OD value of each well was immediately detected at 450 nm using an ELISA Analyzer (Shenzhen Sinothinker Technology Co., Ltd., Shenzhen, China) to calculate the concentrations of IFN- γ , IL-6, IL-10 and TNF- α .

Statistical analysis. The SPSS 19.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis, and Graph Pad Prism 7 was used to plot data images. The measurement data are expressed as mean \pm standard deviation (mean \pm SD), and independent samples t-test was used to compare the measurements between groups. The countable data were expressed as case number/percentage [n (%)], and Chi-square test was used to compare the countable data between groups. One-way analysis of variance was used for the comparison between the mean values of multiple groups, Dunnett-t test was used

Table I. Baseline data of patients in the three groups [n (%)]/(mean \pm SD).

Classification	Group A (n=41)	Group B (n=39)	Group C (n=40)	F/ χ^2 value	P-value
Sex				0.704	0.706
Male	29 (70.73)	27 (69.23)	25 (62.50)		
Female	12 (29.27)	12 (30.77)	15 (37.50)		
Age (years)	36.15 \pm 10.63	34.14 \pm 11.42	33.09 \pm 9.15	0.9	0.409
CSF pressure (mmH ₂ O)				68.991	<0.001
\geq 180	36 (87.80)	33 (84.62)	3 (7.50)		
<180	5 (12.20)	6 (15.38)	37 (92.50)		
Clinical manifestation				11.093	0.02
Headache	29 (70.73)	25 (64.10)	0 (0.00)		
Fever	31 (75.61)	28 (71.79)	8 (20.00)		
Nausea, vomiting	24 (58.54)	26 (66.67)	4 (10.00)		
Consciousness disorder	19 (46.34)	18 (46.15)	0 (0.00)		
CSF appearance				4.059	0.227
Colorless	37 (90.24)	37 (94.87)	40 (100.00)		
Slightly red	2 (4.88)	1 (2.56)	0 (0.00)		
Yellow	2 (4.88)	1 (2.56)	0 (0.00)		
CSF leukocyte ($\times 10^6$ /l)				43.862	<0.001
\leq 8	8 (19.51)	14 (35.90)	36 (90.00)		
>8	33 (80.49)	25 (64.10)	4 (10.00)		
CSF glucose (mmol/l)				33.248	<0.001
<2.8	24 (58.54)	26 (66.67)	3 (7.50)		
2.8-4.5	17 (41.46)	13 (33.33)	37 (92.50)		
CSF chloride (mmol/l)				48.74	<0.001
120-130	12 (29.27)	12 (30.77)	39 (97.50)		
<120	29 (70.73)	27 (69.23)	1 (2.50)		
CSF protein				6.733	0.014
Normal	8 (19.51)	8 (20.51)	1 (2.50)		
Elevated	33 (80.49)	31 (79.49)	39 (97.50)		

for pairwise comparison afterwards. ROC curve was established, the AUC under the ROC curve of IFN- γ , IL-6, IL-10 and TNF- α concentrations in CSF was determined, and the sensitivity and specificity under the diagnostic cut-off were calculated. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

General data. There was no significant difference in sex, age and CSF appearance between group A, group B and group C ($P > 0.05$). By contrast, there were significant differences in clinical manifestations, CSF pressure, CSF leukocyte count, CSF glucose, CSF chloride and CSF protein between the three groups ($P < 0.05$). In group A, 36 cases (87.80%) had CSF pressure ≥ 180 mmH₂O, 29 cases (70.73%) developed headache, 31 cases (75.61%) developed fever, 24 cases (58.54%) developed nausea and vomiting, 19 cases (46.34%) developed consciousness disorder, 33 cases (80.49%) had CSF leukocyte count $> 8 \times 10^6$ /l, 24 cases (58.54%) had CSF glucose < 2.8 mmol/l, 29 cases (70.73%) had CSF chloride < 120 mmol/l, and 33 cases (80.49%)

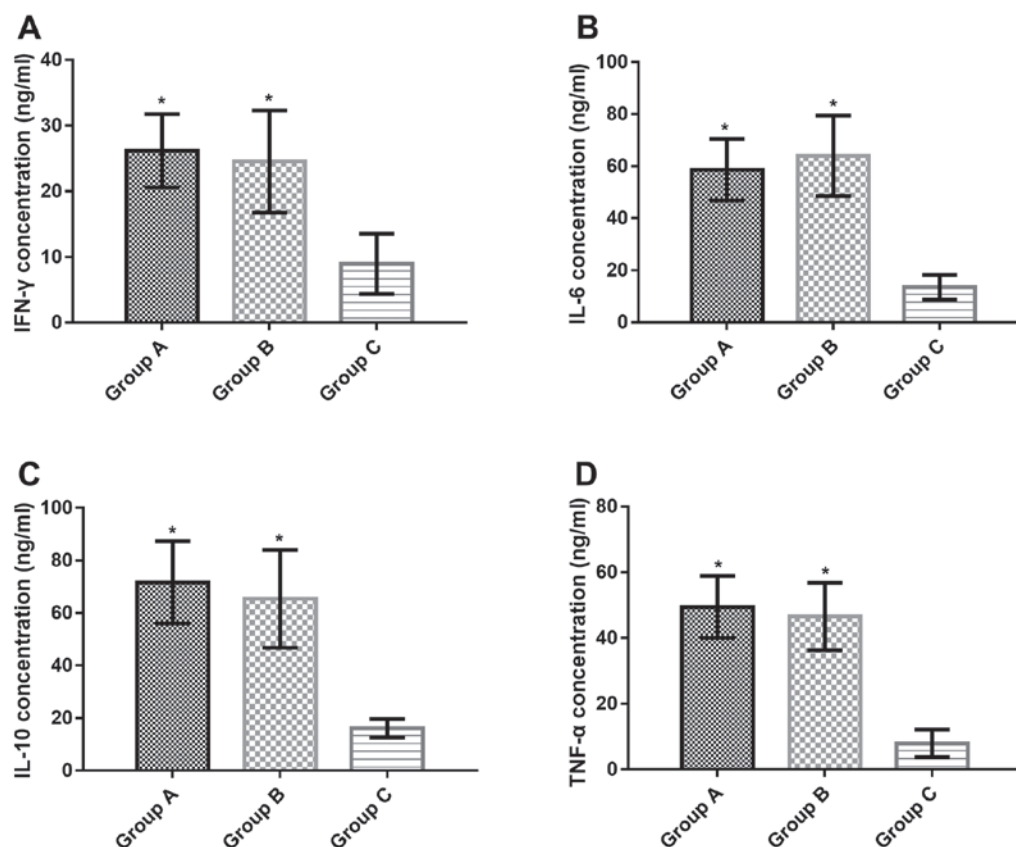
had CSF protein elevation. The numbers of the above indicators in group B were 33 (84.62%), 25 (64.10%), 28 (71.79%), 26 (66.67%), 18 (46.15%), 25 (64.10%), 26 (66.67%), 27 (69.23%), and 31 (79.49%), respectively (Table I).

Concentration of IFN- γ , IL-6, IL-10 and TNF- α in CSF of patients in the three groups. Compared with group C, IFN- γ concentration in CSF of groups A and B increased significantly ($t = 14.980$, $P < 0.001$; $t = 10.930$, $P < 0.001$), IL-6 concentration increased significantly ($t = 22.390$, $P < 0.001$; $t = 19.750$, $P < 0.001$), IL-10 concentration increased significantly ($t = 17.18$, $P < 0.001$; $t = 16.450$, $P < 0.001$), TNF- α concentration increased significantly ($t = 25.290$, $P < 0.001$; $t = 22.070$, $P < 0.001$). There was no significant difference in IFN- γ , IL-6, IL-10 and TNF- α concentrations in CSF of groups A and B ($P > 0.05$) (Table II and Fig. 1).

Concentration of IFN- γ , IL-6, IL-10 and TNF- α in CSF of patients in the improvement group and the death group. The concentration of IL-6, IL-10 and TNF- α in CSF of patients in the improvement group was significantly lower than those in

Table II. Comparison of IFN- γ , IL-6, IL-10 and TNF- α concentration in CSF of three groups of patients (mean \pm SD).

Group	n	IFN- γ (ng/ml)	IL-6 (ng/ml)	IL-10 (ng/ml)	TNF- α (ng/ml)
Group A	41	26.17 \pm 5.58	58.63 \pm 11.79	71.63 \pm 20.13	49.43 \pm 9.48
Group B	39	24.53 \pm 7.78	63.97 \pm 15.45	65.41 \pm 18.63	46.58 \pm 10.28
Group C	40	8.97 \pm 4.59	13.52 \pm 4.78	16.13 \pm 3.47	7.93 \pm 4.17
F value	-	96.800	230.900	185.200	303.900
P-value	-	<0.001	<0.001	<0.001	<0.001

Figure 1. Comparison of IFN- γ , IL-6, IL-10 and TNF- α concentration in CSF of three groups of patients. Comparison of (A) IFN- γ , (B) IL-6, (C) IL-10 and (D) TNF- α concentration in CSF between the three groups of patients. *P<0.001 compared with group C.

the death group ($t=3.534$, $P<0.001$; $t=3.460$, $P<0.001$; $t=3.557$, $P<0.001$), while the IFN- γ concentration was increased significantly ($t=4.904$, $P<0.001$) (Table III and Fig. 2).

ROC curve of IFN- γ , IL-6, IL-10 and TNF- α concentration in CSF for diagnosing the prognosis of AIDS patients with CNS infection. ROC curve of IFN- γ , IL-6, IL-10 and TNF- α concentration in CSF for diagnosing prognosis of AIDS patients with CNS infection was plotted. The AUC, diagnostic sensitivity, specificity, and optimal cut-off value of IFN- γ in diagnosing prognosis of AIDS patients with CNS infection were 0.795 (95% CI: 0.694-0.896), 89.29, 66.67, and 25.41%, respectively. While those of IL-6 were 0.760 (95% CI: 0.643-0.876), 83.93, 62.50 and 59.80%, respectively. Those of IL-10 were 0.780 (95% CI: 0.660-0.901), 67.86, 87.50, and 76.38%, respectively. Those of TNF- α were 0.734 (95% CI: 0.604-0.863), 58.93, 83.33, and 55.82%, respectively (Table IV and Fig. 3).

Discussion

HIV belongs to retroviruses and is the pathogen of AIDS, both neurotropic and lymphotropic. HIV invades T lymphocytes and multiplies in a large number of helper CD4⁺ lymphocytes, resulting in a large number of their progressive reductions, further leading to serious damage to the immune function of the organism, which may cause opportunistic infections (15,16). HIV can infect B lymphocytes, bone marrow stem cells and mononuclear phagocytes simultaneously. CNS is the vacuum area of body immunity, and tuberculosis and cryptococcosis are common opportunistic infections of AIDS (17). Tuberculous meningitis caused by mycobacterium tuberculosis infection and cryptococcal meningitis caused by cryptococcal neoformans infection are the most common types of CNS infection in AIDS patients. Delays in treatment caused by untimely diagnosis of CNS infection are the main causes of AIDS deaths (18,19).

Table III. Comparison of IFN- γ , IL-6, IL-10 and TNF- α concentrations in CSF of patients between the improvement group and the death group (mean \pm SD).

Group	n	IFN- γ (ng/ml)	IL-6 (ng/ml)	IL-10 (ng/ml)	TNF- α (ng/ml)
Improvement group	56	30.36 \pm 4.62	58.64 \pm 10.67	64.23 \pm 12.43	45.23 \pm 8.64
Death group	24	24.37 \pm 5.16	67.73 \pm 10.23	76.84 \pm 19.68	53.37 \pm 10.95
t value	-	4.904	3.534	3.460	3.557
P-value	-	<0.001	<0.001	<0.001	<0.001

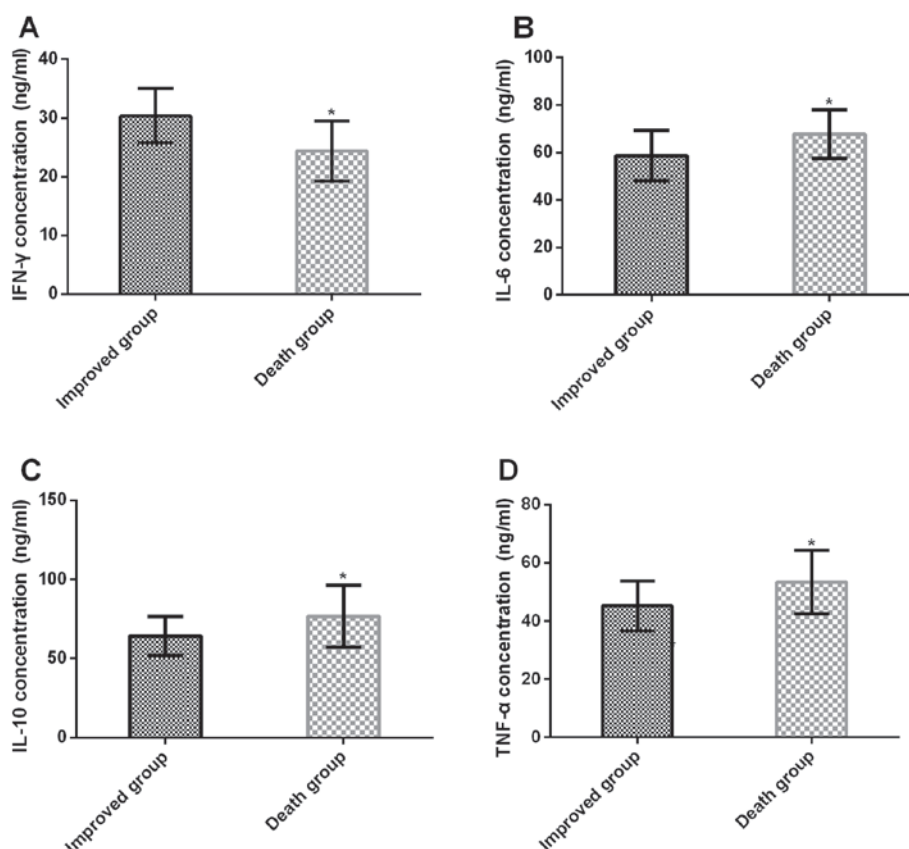


Figure 2. Comparison of IFN- γ , IL-6, IL-10 and TNF- α concentrations in CSF of patients between the improvement group and the death group. Comparison of (A) IFN- γ , (B) IL-6, (C) IL-10 and (D) TNF- α concentration in CSF between the improvement and death groups. *P<0.001 compared with the improvement group.

Once the body has immune deficiency, the integrity of the blood-brain barrier is destroyed by HIV, which facilitates the intracranial spread of mycobacterium tuberculosis and cryptococcus neoformans, resulting in CNS infection in the body. CSF undergoes corresponding pathological changes when CNS infection occurs (20). In the study of Price *et al* (21), it was pointed out that there were difficulties in the clinical diagnosis and management of HIV-related CNS infection, while changes in CSF biomarkers could provide an objective and valuable evaluation method. The results of this study showed that both group A and group B patients presented with clinical manifestations of meningitis such as headache, fever, nausea, vomiting and consciousness disorder. In group A, 87.80% of patients had intracranial pressure \geq 180 mmH₂O, 80.49% had leucocyte count $>8 \times 10^6/l$, 58.54% had glucose <2.8 mmol/l, 70.73% had chloride <120 mmol/l, and 80.49% had protein

elevation; while the rate of those 5 biochemical components of CSF in the group B were 84.62, 64.10, 66.67, 69.23, and 79.49%, respectively. The significant changes of CSF biochemical indexes after CNS infection may be caused by the infection of mycobacterium tuberculosis and cryptococcus neoformans, causing an increase of permeability of choroid plexus capillaries and meninges, leading to the increase of protein and intracranial pressure and the decrease of glucose and chloride. Graybill *et al* (22) pointed out that the increased intracranial pressure and decreased glucose content were the main reasons for the poor prognosis of patients. Therefore, by observing the clinical symptoms of AIDS patients with CNS infection and the changes of CSF biochemical indexes, timely drug symptomatic treatment can be given.

Mycobacterium tuberculosis, viruses and fungi infections can cause T-helper 1 (Th1) mediated cellular immune response

Table IV. Diagnostic value of IFN- γ , IL-6, IL-10 and TNF- α concentration in CSF in patients with AIDS complicated with CNS infection.

Diagnostic index	AUC	95% CI	Standard error	Cut-off	Sensitivity (%)	Specificity (%)
IFN- γ	0.795	0.694-0.896	0.051	25.41	89.29	66.67
IL-6	0.760	0.643-0.876	0.060	59.80	83.93	62.50
IL-10	0.780	0.660-0.901	0.062	76.38	67.86	87.50
TNF- α	0.734	0.604-0.863	0.066	55.82	58.93	83.33

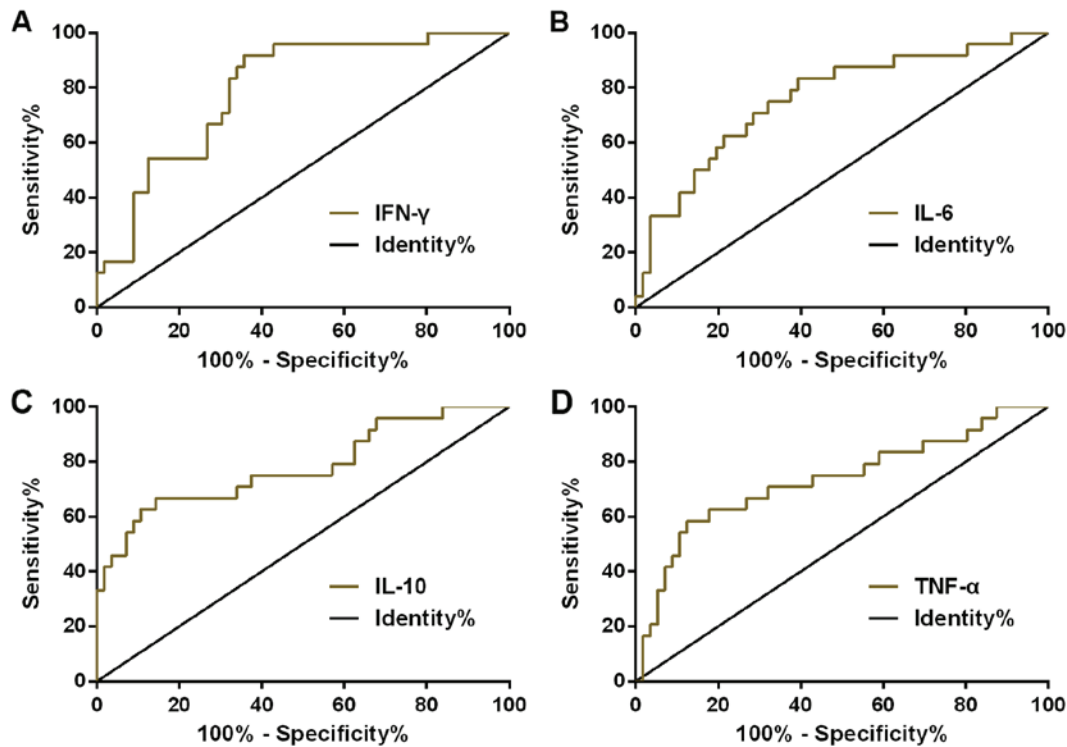


Figure 3. ROC curve of IFN- γ , IL-6, IL-10 and TNF- α concentrations in CSF for diagnosing the prognosis of AIDS patients with CNS infection. ROC curve of (A) IFN- γ , (B) IL-6, (C) IL-10 and (D) TNF- α in diagnosing the prognosis of AIDS patients with CNS infection.

in humans, while cellular immunity plays an important role in resisting pathogen infection (23). HIV infection is a disorder of immune function characterized by reduction of CD4⁺ T cells, imbalance of cytokines and activation of polyclonal cells, and cytokines play an important role in balancing and maintaining immune response (24). IFN- γ , IL-6, IL-10, TNF- α and other cytokines are secreted by activated Th1 cells, Th2 cells, B cells and other cells, which mediate the immune responses of body fluids (25). In a study by Chakrabarti *et al* (26), the levels of inflammatory cytokines and chemokines IL-6, IL-8/CXCL 8, IP-10/CXCL 10, TNF- α in patients infected with AIDS and Mycobacterium tuberculosis increased, and soluble IL-2 receptors were released after activation of CD4⁺ T cells in the patients. These inflammatory cytokines and chemokines had very important effects on the development of the disease. The results of this study showed that the concentrations of IFN- γ , IL-6, IL-10 and TNF- α in CSF of patients in group A and B were significantly higher than those in group C, suggesting their involvement in the inflammatory reaction and immune response of AIDS complicated with tuberculous meningitis

and cryptococcal meningitis, which is similar to previous studies. Clinically, selectively blocking HIV infected patients can up-regulate the secretion of HIV-1 expressing cytokines, implement cytokines to rebuild the immune function of the body's defect, stimulate the recovery and improve the immune imbalance, which is an important strategy for the treatment of AIDS (27). A study by Worsley *et al* (28) showed that, the severity of HIV was manifested through the reduction of CD4⁺ T cells and the occurrence of opportunistic infections; the levels of IL-10 mRNA and TNF- α mRNA increased with the aggravation of the disease, and the decrease of IFN- γ mRNA was one of the reasons leading to the deterioration of HIV disease; with the increase of virus replication, the levels of TNF- α , IL-4 and IL-10 increased and IFN- γ decreased, making children vulnerable to HIV-related opportunistic infections. In our study, the levels of IL-6, IL-10 and TNF- α in CSF of the patients in the improvement group were significantly lower than those in the death group, while the levels of IFN- γ increased significantly, indicating that they may be involved in the development of AIDS patients with CNS infection and

related to the patients' poor prognosis. The ROC curve of IFN- γ , IL-6, IL-10 and TNF- α in the diagnosis of AIDS patients with CNS infection was further evaluated, and the results indicated their certain values in the diagnosis of AIDS patients with CNS infection. Therefore, detecting the concentrations of IL-6, IL-10 and TNF- α in CSF of AIDS patients with CNS infection has certain predictive value for the poor prognosis of the patients.

In this study, the subjects were screened strictly according to the inclusion and exclusion criteria. The collection of samples and the detection of cytokines were the same in methodology, eliminating the differences caused by experimental methods and ensuring the rigor and reliability of this study. Among CNS infections, the expression levels of cytokines in AIDS patients infected with different severity levels may be different, and the network formed by cytokines is extremely complex, with mutual regulation and interaction (29). The regulatory mechanism of cytokines in AIDS complicated with CNS infection was not included in this study. Future study should expand the sample size, and group the course and treatment of patients with different severity of infection.

Collectively, AIDS patients with tuberculous meningitis and cryptococcal meningitis in CNS infection diseases are mainly manifested by headache, fever, nausea, vomiting, and consciousness disorder. CSF biochemistry is characterized by increased pressure, leucocyte count and protein, and decreased chloride and glucose. IFN- γ , IL-6, IL-10 and TNF- α in CSF have certain predictive value for poor prognosis of AIDS patients with CNS infection.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

ZC wrote the manuscript. ZC and NW were responsible for ELISA. YH analyzed and interpreted the patients' data. MW assisted with statistical analysis. All the authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of The First Hospital of Changsha (Changsha, China). Patients who participated in this research had complete clinical data. Signed written informed consents were obtained from the patients and/or the guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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