The clinical value of cerebrospinal fluid of Notch1 of DLL1 detection of infectious diseases of the central nervous system

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ABSTRACT: TB meningitis is a common clinical infectious diseases of the central nervous system. Select Diagnostics clear initial treatment of infectious diseases of the central nervous system in patients using enzyme-linked immunosorbent assay for the quantitative determination in patients with CSF soluble Notch1, DLL1 content: CSF soluble DLL1 content, knot the brain was significantly higher thanother groups, so as a new indicator soluble Notch1, DLL1 detection in the diagnosis of tuberculous meningitis and evaluation of treatment effect may have important clinical value.
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Key Words: Delta-like-ligand-1; Notch1; tuberculous meningitis; cerebrospinal fluid

1. Introduction

Tuberculous meningitis is one of the common clinical infectious diseases of the central nervous system, the correct diagnosis, early treatment is to determine the most important prognostic factors. Our previous studies have found in the cerebrospinal fluid of patients with tuberculous meningitis (cerebrospinal fluid, CSF) and serum soluble Delta-like-1 (DLL1) levels were significantly increased [1-5], and Notch ligands DLL1 as its accelerated shedding help the Notch signal transduction. Therefore, the study on the basis of the original study, the diagnosis of infectious diseases through the detection of the central nervous system in patients with cerebrospinal fluid (CSF) soluble Notch1 and DLL1 content, and explore new tuberculous meningitis.

2 objects and methods

2.1 The study selected 348 cases of the First Affiliated Hospital of Zhengzhou University, Department of Neurology, infectious disease of the central nervous system in July 2009 -2012 in March, are in strict accordance with the relevant standard to confirm the diagnosis. Patients with tuberculous meningitis 127 cases, as the case group, 66 males and 61 females, aged 11-65 years, mean 48 ± 16.5 years; purulent meningitis in 10 cases, 65 cases of viral meningitis, Cryptococcus neoformans 15 cases of meningitis, a total of 90 cases, as the brain (film) inflammation control group, male 53 cases, female 50 cases, aged 8-73 years old, with an average of 23.3 ± 16.2 years old; same period Check the infection of the central nervous system in healthy controls 72 cases, as a non-infected control group, male 42 cases, 30 females, aged 8-76 years, mean 30.4 ± 17.1 years.

2.2 tuberculous meningitis diagnostic criteria: (1) age> 12 years of age, 33 patients according to Ahuja of TMB diagnostic criteria (Ahuja standard): (A) clinical: the performance of the fever and headache> 14d (prerequisites), vomiting, sensory changes or partial deletion (prerequisite). (B) CSF: lymphocytosis (> 20 × 106 / L), lymphocyte predominant (> 60%), protein excretion> 1g / L glucose <glycemic × 60%, the cryptococcosis and malignant cells tested negative. (C) head imaging tests check in accordance with the following two or more: ① the base of the lymphatic clearance or sylvian fissure and oozing; (2) hydrocephalus; ③ cerebral infarction; ④ gyri enhanced. Tuberculosis performance outside the nervous system (D): radiological or bacteriological examination of the evidence, or histopathological examination are the caseous necrosis active tuberculosis, tuberculosis, gastrointestinal, genitourinary tract tuberculosis, lymph node tuberculosis, bone tuberculosis or cutaneous tuberculosis. Height may TBM is required to have (A), (B), (C), (D) 4; may TBM required to have (A), and includes (B), (C), (D) in any of two ; perhaps TBM need to have (A), and equipped (B), (C), (D) in any one. (2) age ≤ 12 years of age in 13 patients with reference standard of Seth and Sharma (Seth standard): the fever instead Ahuja (A) standard> 14d; (D) in the positive history of exposure to tuberculosis or TB hormone test (1TU, induration diameter> 10mm)-positive can be considered to comply with this provision.

2.3 Research Methods

(1). Specimens were taken: in the case of the informed consent of patients or their families, to retain in CSF specimens 2 mL sterile lumbar

puncture to obtain CSF specimens vacuum blood collected without anticoagulant, placed in a 80 ℃ refrigerator. Dynamic observation of patients with tuberculous meningitis specimens after treatment at different times CSF 2mL CSF specimens sterile lumbar puncture to obtain, placed in a 80 ℃ refrigerator.

(2) detection indicators and methods: enzyme-linked immunosorbent assay (ELISA) and quantitative determination of human CSF soluble Notch1, DLL1 content. The Notch1 kit provided by Roche the DLL1 kit from Korea AdipoGen, provide. In strict accordance with the kit instructions.

2.4 statistical methods used SPSSl7.0 software, for statistical analysis. Normal distribution measurement data are expressed as mean ± standard deviation ($\bar{x}$ ± s) denotes. Between groups using analysis of variance (F test) between any two groups using the Bonferroni method; two groups were compared using the Wilcoxon rank sum test. P <0.05 statistically significant difference.

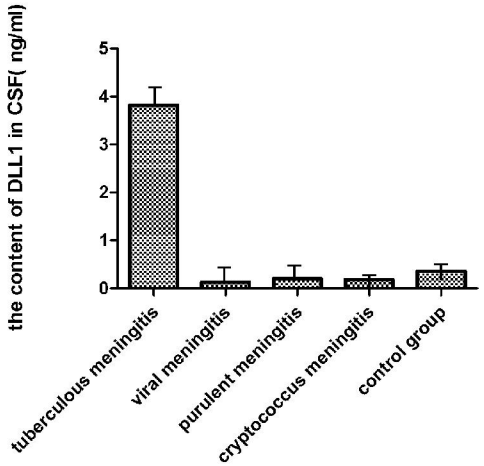
3 Results

3.1 CSF soluble DLL1 content, prompted in Table 1, the tuberculous meningitis group was significantly higher than the other groups (P <0.01); judgment value as tuberculous meningitis DLL1 ≥ 0.77 ng / ml, with a sensitivity of 100%, a specificity of 96.9%, the ROC curve of 0.951. Between the other groups there was no significant difference (P> 0.05).

Table 1. Comparison of the CSF in each group DLL1 content (ng / ml) of ($\bar{x}$ ± s)

Group	cases	Notch1 $\bar{x}$ ±s	Notch>8.5pg/ml cases	Notch>8.5pg/ml (%)	P values
Tuberculous meningitis group	127	7.65±0.32	95	74.8	
Viral meningitis group	65	1.21±0.12	0	0	0.000
Meningitis group	10	1.30±0.15	0	0	0.000
Cryptococcal meningitis group	15	6.65±0.07	11	73.3	0.011
Non-infected control group	72	0.95±0.25	0	0	0.000

Note: P value tuberculous meningitis group compared with the other groups



3.2 CSF soluble a Notch1 content, Table 2 prompts, tuberculous meningitis group was significantly higher than the other groups (P <0.01); judgment of tuberculous meningitis to Notch1 ≥ 8.50pg/ml as, a sensitivity of 86.8% and a specificity of 85.2%, the ROC curve of 0.866, but this standard for cryptococcal encephalitis distinguish poor compared between the other groups were not significantly different (P> 0.05).

Table 2 Comparison of CSF in Notch1 content (pg / ml) ($\bar{x}$ ± s)

Group	The number of cases	Notch1 $\bar{x}$ ±s	Notch>8.5pg/ml cases	Notch>8.5pg/ml (%)	P values
Tuberculous meningitis group	127	7.65±0.32	95	74.8	
Viral meningitis group	65	1.21±0.12	0	0	0.000
Meningitis group	10	1.30±0.15	0	0	0.000
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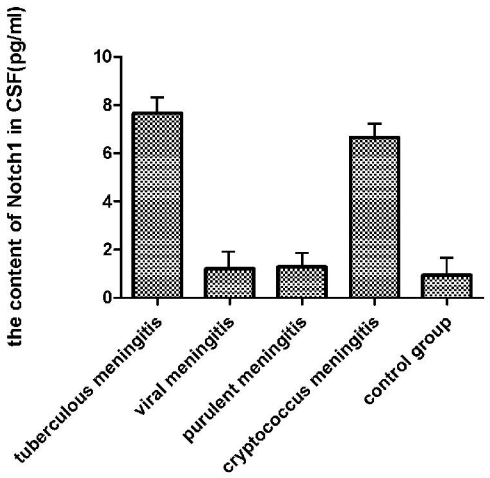


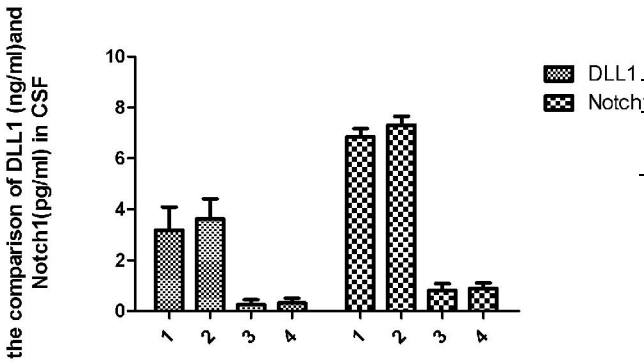
3.3 high ester associated with hyperlipidemia or not CSF soluble of Notch-1, the DLL1 the content (ng / ml) measurement results: According to Table 3 prompted, CSF associated with high ester hyperlipidemia group Nocth1 tuberculous meningitis, tuberculous meningitis with normal triglycerides group (6.85 ± 0.32,7.30 ± 0.35), both compared with no significant difference (P> 0.05); the CSF in Nocth1 non-infected partners the high ester hyperlipidemia group, non-infection with normal triglyceride group were (0.81 ± 0.27,0.89 ± 0.21), both compared to no significant difference (P> 0.05), tuberculous meningitis with CSF in DLL1 the high ester hyperlipidemia group, knot brain associated with normal triglyceride group (3.18 ± 0.92, respectively. , 3.62 ± 0.79), both showed no significant difference (P> 0.05); CSF in DLL1 non-infection with the high ester hyperlipidemia group

and non-infection with normal triglyceride group (0.25 ± 0.20,0.31 ± 0.19, respectively), both compared to no significant difference (P> 0.05).

Table 3 Comparison of groups in CSF of DLL1 (ng / ml) and Notch 1 levels (pg / ml) ($\bar{x} \pm s$)

Group	cases	DLL1	Nocth1	P values
Tuberculous meningitis with hyperlipidemia group	27	3.18±0.92	6.85±0.32	
Tuberculous meningitis control group	100	3.62±0.79	7.30±0.35	*P*<0.05
Non-infected control with hyperlipidemia group	35	0.25±0.20	0.81±0.27	*P*<0.05
Non-infected control group	37	0.31±0.19	0.89±0.21	*P*<0.05

Note: P value tuberculous meningitis with hyperlipidemia group compared with the other groups



1 Tuberculous meningitis with hyperlipidemia group
2 Tuberculous meningitis control group
3 Non-infected control with hyperlipidemia group
4 Non-infected control group

3.4 Western Blot method: Figure 1,2 prompted tuberculous meningitis in CSF Notch1, DLL-1 expression in other groups of patients rarely expressed.

Figure 1 the group of in CSF DLLI, expression Tuberculous meningitis group disease brain group the Brain group of cryptococcal meningitis group normal group

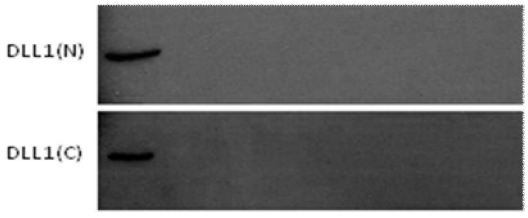


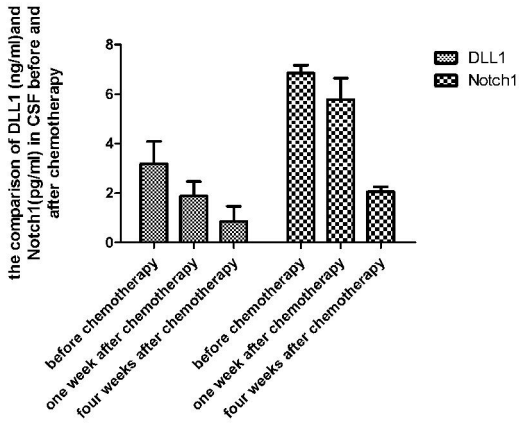
Figure 2 the group of in CSF Nocth1, expression Tuberculous meningitis group disease brain group the Brain group of cryptococcal meningitis group normal group

3.5 Table 4 suggest that the follow-up of patients found 37 cases of tuberculous meningitis, effective chemotherapy for one week, CSF soluble Sexual DLL1, Notch1 levels were significantly decreased (1.89 ± 0.58,5.78 ± 0.87), both significant differences (P <0.05), and 4 weeks of treatment can be reduced to normal level (0.85 ± 0.62,2.05 ± 0.21), two compared with a significant difference (P <0.05).

Table 4. Comparison between before and after chemotherapy

Group	The number of cases	DLL1	Notch1	P values
Before chemotherapy	37	3.18±0.92	6.85±0.32	
One week after chemotherapy	37	1.89±0.58	5.78±0.87	P<0.05
After four weeks of chemotherapy	35	0.85±0.62	2.05±0.21	P<0.05

Note: P value compared with the other groups before chemotherapy



4 Discussion

Mycobacterium tuberculosis genome contains more than 4000 genes, 250 genes encoding fatty acid metabolism enzyme the mycolic acid the biggest fatty acids in the natural world, the ability to escape the immune system to attack it and virulence of Mycobacterium tuberculosis, Mycobacterium tuberculosis closely related to [6], the evidence shows the the Mycobacterium tuberculosis importance of fat metabolism. Notch signaling pathway play an important role in the regulation of cell differentiation and cell fate decisions the, DLLl Drosophila Notch ligand Delta human homologue of the body is composed of 723 amino acids L-type transmembrane proteins [7]. Peroxisome proliferator-activated receptor γ (peroxisomal proliferator-activated receptors δandγ, PPARγ) is a very

important member of the family of nuclear receptors in the transcriptional regulation of fat cells that have the most important function [8]. Carmen Garce 's study found that the use of hormone-induced 3T3-L1 fibroblasts to adipocyte differentiation, Notch1 play an important role in the inhibition of Notch1 expression by antisense Notch1 structure or interference interaction Notch/DLL1 further reduce the expression of PPARγ thereby significantly inhibit 3T3-L1 fibroblast cells [9] to the fat cell differentiation. The Notch ligands DLL1 Notch receptor activation of the Notch signaling pathway, to determine the fate of adipocyte differentiation, involved in the regulation of fat metabolism. Based on the above theoretical speculation, Tuberculosis (TB) is a chronic wasting disease, caused by fat metabolism, the presence of the excessive differentiation of fat cells; accelerate as the Notch ligands DLL1 shedding helps Notch signaling promotes adipocyte differentiation.

This study suggests that patients with tuberculous meningitis CSF Notch1 and DLL1 content were significantly higher, and its mechanism is not fully understood, In addition to the aforementioned DLL1 excessive shedding helps Notch signaling in promoting differentiation of fat cells, may also involvethe following mechanisms: (1) Mycobacterium tuberculosis by inhibition of macrophage activation signaling pathway and thus in a large number of host immune response survival. Combined mycobacterial infection of the host cell, by upregulating the expression of Notch1 in activation of the Notch signaling pathway, thereby promoting cytokine signaling to inhibit sub 3 (SOCS3) expression [10]; SOCS3 is induced by a variety of cytokines and Toll-like receptor negative regulator of the signaling pathway by inhibiting the activation of macrophages in IFN-γ-dependent JAK / STAT signaling pathway, thereby reducing the mobilization of macrophages [11,12].2) TB infection, T-cell-mediated cellular immunity is an important protective immune response in the bone marrow, the Notch signaling pathway can significantly inhibit the differentiation of hematopoietic stem cell lines to B promote T cell segmentation [7,13]; CD4 T cells recognize human histocompatibility antigen Ⅱ (MHC Ⅱ) Mycobacterium tuberculosis antigen presenting peptide fragments further activate the formation of helper T cells (Th1 cells) and Th1 cells secrete IL-2 and IFN-γ, TNF-α, mainly mediated cytotoxicity and local inflammatory immune response, the secondary antibody-producing immune cells involved in M. tuberculosis bacteria. The study found that when the CD4 T cell activation the Notch1 and CD4 coexist on the cell surface [14], and Notch by its ligand DLL1 interaction promote CD4 T cells differentiate into Th1 cells [15].

This study was a joint detection in CSF NOTCH ligand DLL1 content, an important reference significance for the diagnosis and differential diagnosis of a variety of central nervous system infection, and simple method might as tuberculous meningitis valuable diagnostic substances.

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