

艾滋病合并隐球菌性与结核性脑膜炎多重感染的临床及影像学特征分析

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【摘要】 目的 探究艾滋病(aquired immunodeficiency syndrome, AIDS)合并隐球菌性脑膜炎(cryptococcal meningitis, CM)与结核性脑膜炎(tuberculous meningitis, TBM)多重感染患者的临床与MRI影像特点,为临床诊治提供参考。**方法** 回顾性分析上海市公共卫生临床中心2015年9月至2021年10月收治的39例艾滋病合并隐球菌性与结核性脑膜炎(AIDS/CM/TBM)患者的临床资料,并比较其与61例艾滋病合并隐球菌性脑膜炎(AIDS/CM)患者和42例艾滋病合并结核性脑膜炎(AIDS/TBM)患者的临床表现、实验室指标及头颅MRI影像特征等方面的差异。**结果** AIDS/CM/TBM组患者头痛的发生率高于AIDS/TBM组,抽搐、视力障碍、意识障碍的发生率高于AIDS/CM组和AIDS/TBM组,差异均有统计学意义($P<0.05$)。32例(82.0%)AIDS/CM/TBM患者CD4⁺T淋巴细胞计数 ≤ 100 个/ μL 。AIDS/CM/TBM组白细胞计数、脑脊液蛋白水平平均高于AIDS/CM组,脑脊液糖水平低于AIDS/CM组;脑脊液压力和脑脊液氯化物水平高于AIDS/TBM组,差异均有统计学意义($P<0.05$)。34例(87.2%)AIDS/CM/TBM患者头颅MRI检查存在病灶,多发为主,呈脑膜炎和脑膜脑炎表现,脑叶病灶发生率高于AIDS/CM组,血管周围间隙扩大或胶样假囊的出现率低于AIDS/CM组,差异均有统计学意义($P<0.05$)。多因素Logistic回归分析结果显示头痛、意识障碍及脑脊液糖 ≤ 1.85 mmol/L与AIDS/CM/TBM多重感染相关($P=0.009, 0.005, 0.002$)。**结论** AIDS/CM/TBM临床表现更重,实验室检查变化更显著,头颅MRI表现以脑膜炎和脑膜脑炎为主;头痛、意识障碍及脑脊液糖 ≤ 1.85 mmol/L对其诊断具有提示意义,有助于临床及时干预。**【关键词】** 艾滋病(AIDS); 隐球菌性脑膜炎(CM); 结核性脑膜炎(TBM); 多重感染; 鉴别诊断**【中图分类号】** R445.2 **【文献标志码】** A **doi:** 10.3969/j.issn.1672-8467.2022.04.004

Analysis of clinical and imaging characteristics of cryptococcal meningitis and tuberculous meningitis co-infection in AIDS patients

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【Abstract】 Objective To investigate the clinical and MRI characteristics of cryptococcal meningitis and tuberculous meningitis co-infection in aquired immunodeficiency syndrome (AIDS) patients, and to improve its diagnostic efficacy. **Methods** The clinical data of 39 AIDS patients with cryptococcal meningitis and tuberculous meningitis co-infection (AIDS/CM/TBM) who were admitted to Shanghai Public Health Clinical Center from Sept 2015 to Oct 2021 were retrospectively analyzed. Their clinical manifestations, laboratory results and MRI findings were compared with 61 AIDS patients with cryptococcal meningitis (AIDS/CM) and 42 AIDS patients with tuberculous meningitis (AIDS/TBM).

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Results The incidence rate of headache of the AIDS/CM/TBM patients was higher than that of the AIDS/TBM patients, and the incidence rate of convulsion, visual disorders, consciousness disorders were higher than those in the AIDS/CM patients and AIDS/TBM patients ($P<0.05$). The $CD4^+$ T cell counts of 32 (82.0%) AIDS/CM/TBM patients were ≤ 100 cells/ μ L. The white blood cell counts and the cerebrospinal fluid (CSF) protein levels in the AIDS/CM/TBM patients were significantly higher than those in the AIDS/CM patients, and the CSF glucose levels were significantly lower than those in the AIDS/CM patients ($P<0.05$). The CSF opening pressure and the CSF chloride levels in the AIDS/CM/TBM patients were significantly higher than those in the AIDS/TBM patients ($P<0.05$). Thirty-four (87.2%) AIDS/CM/TBM patients showed intracranial lesions in MRI examination, and the main manifestations were meningitis and meningoencephalitis. The incidence of brain lobe lesions in the AIDS/CM/TBM patients was higher than that of the AIDS/CM patients, and the incidence of dilated Virchow-Robin spaces (VRS) or pseudocysts was lower than that of the AIDS/CM patients ($P<0.05$). Multivariate Logistic regression analysis showed that headache, consciousness disorders, and CSF glucose levels ≤ 1.85 mmol/L were correlated with the multiple infection of AIDS/CM/TBM ($P=0.009, 0.005, 0.002$). **Conclusion** The clinical manifestations of AIDS/CM/TBM are more severe, the changes of laboratory examination are more significant, and the manifestations of brain MRI are meningitis and meningoencephalitis. Headache, consciousness disorders, and CSF glucose levels ≤ 1.85 mmol/L have suggestive significance for clinical diagnosis, which are helpful for timely intervention.

【Key words】 acquired immunodeficiency syndrome (AIDS); cryptococcal meningitis (CM); tuberculous meningitis (TBM); co-infection; differential diagnosis

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艾滋病(acquired immunodeficiency syndrome, AIDS)患者因免疫系统破坏,免疫功能严重下降,极易发生各种机会性感染,10%~20%的AIDS患者以中枢神经系统感染为首发症状^[1]。隐球菌性脑膜炎(cryptococcal meningitis, CM)和结核性脑膜炎(tuberculous meningitis, TBM)是AIDS患者常见的两种中枢神经系统机会性感染,也是主要的死亡原因^[2]。两者临床表现相似,缺乏特异性^[3],CM病原学检查敏感度可达90%^[4],而TBM病原学检查灵敏性不佳^[5],极大地限制了AIDS/CM/TBM多重感染早期诊断的准确性,导致漏诊误治,延误治疗时机。有研究报道,AIDS/CM患者常可合并结核感染,且与死亡风险增加有关^[6]。目前国内外AIDS患者合并CM与TBM多重感染的报道较少,本研究通过对比分析AIDS合并CM与TBM(AIDS/CM/TBM)患者、AIDS合并CM(AIDS/CM)患者和AIDS合并TBM(AIDS/TBM)患者的临床资料,总结AIDS/CM/TBM的临床及头颅MRI表现特征,以期为临床医师提供诊治思路。

资 料 和 方 法

研究对象 收集整理上海市公共卫生临床中心2015年9月至2021年10月收治的AIDS合并中枢神经系统感染患者的临床资料,从中筛选出AIDS/CM/TBM患者39例,AIDS/CM患者61例,AIDS/TBM患者42例。AIDS诊断符合中华医学会感染病分会艾滋病学组2018年制定的《中国艾滋病诊疗指南》^[1]。CM与TBM诊断符合相应的诊断标准^[7-9]。

研究方法 回顾性分析所有患者的基本资料、感染病史、临床表现、实验室检查指标、头颅MRI检查结果等,对比分析3组患者在临床特征、 $CD4^+$ T淋巴细胞计数、脑脊液实验室检查指标、头颅MRI影像特征等方面存在的差异,探究相关指标在AIDS/CM/TBM诊断中的价值。

统计学分析 采用SPSS 20.0软件进行统计学处理。计数资料以例数和百分数表示,组间比较采

用 χ^2 检验或Fisher确切概率法,多重比较采用Bonferroni校正法。经单样本Kolmogorov-Smirnov检验呈正态分布的计量资料以 $\bar{x}\pm s$ 表示,多组间比较采用单因素方差分析,多重比较采用LSD法;偏正态分布的计量资料以M(P_{25},P_{75})表示,多组间比较采用Kruskal-Wallis H检验,多重比较采用Dwass-Steel-Critchlow-Fligner法。将以上单因素检验具有统计学意义($P<0.05$)的变量纳入多因素Logistic回归分析,其中计量资料通过受试者工作特征曲线确定最佳截断值,转换成二分类变量。

结 果

一般情况 AIDS/CM/TBM组患者平均年龄

(39.7 ± 13.8)岁,男36例、女3例;确诊合并TBM 3例(7.7%),临床诊断合并TBM 36例(92.3%)。AIDS/CM组平均年龄(36.8 ± 11.2)岁,男53例、女8例。AIDS/TBM组平均年龄(40.9 ± 14.9)岁,男40例、女2例;确诊合并TBM 5例(11.9%),临床诊断合并TBM 37例(88.1%)。3组患者间年龄、性别差异无统计学意义。

临床特征 AIDS/CM/TBM组患者头痛的发生率高于AIDS/TBM组,抽搐、视力障碍及意识障碍的发生率高于AIDS/CM组和AIDS/TBM组,差异均有统计学意义($P<0.05$)。AIDS/CM/TBM组合并肺结核的发生率高于AIDS/CM组,AIDS/CM组合并肺隐球菌病的发生率高于其他两组,差异均有统计学意义($P<0.05$,表1)。

表1 3组患者临床特征比较

Tab 1 Comparison of clinical characteristics among the three groups					[n(%)]
Clinical characteristics	AIDS/CM/TBM	AIDS/CM	AIDS/TBM	χ^2	P
Clinical manifestation					
Headache	35 (89.7) ⁽²⁾	49 (80.3) ⁽²⁾	17 (40.5)	28.310	<0.001
Fever	29 (74.4)	43 (70.5)	24 (57.1)	3.144	0.225
Dizziness	17 (43.6)	24 (39.3)	11 (26.2)	2.980	0.221
Vomiting	16 (47.1)	18 (29.5)	7 (16.7)	2.926	0.087
Cough	12 (30.8)	13 (21.3)	13 (31.0)	1.620	0.455
Convulsion	11 (28.2) ⁽¹⁾⁽²⁾	2 (3.3) ⁽²⁾	5 (11.9)	13.386	0.001
Visual disorders	15 (38.5) ⁽¹⁾⁽²⁾	6 (9.8) ⁽²⁾	10 (23.8)	11.560	0.003
Hearing disorder	4 (10.3)	2 (3.3)	3 (7.1)	Fisher exact probability	0.276
Consciousness disorders	13 (33.3) ⁽¹⁾⁽²⁾	7 (11.5) ⁽²⁾	7 (16.7)	7.595	0.023
Dyskinesia	5 (12.8)	3 (4.9)	6 (14.3)	Fisher exact probability	0.214
Complications of pulmonary infection					
Pulmonary cryptococcosis	2 (5.1) ⁽¹⁾⁽²⁾	8 (13.1) ⁽²⁾	0 (0.0)	Fisher exact probability	0.022
Pulmonary tuberculosis	7 (17.9) ⁽¹⁾	2 (3.3) ⁽²⁾	11 (26.2)	11.454	0.003
Pneumocystis pneumonia	1 (2.6)	1 (1.6)	2 (4.8)	Fisher exact probability	0.815

⁽¹⁾Compared with AIDS/CM group, $P<0.05$; ⁽²⁾Compared with AIDS/TBM group, $P<0.05$.

实验室检查 39例AIDS/CM/TBM患者中,32例(82.0%)CD4⁺T淋巴细胞计数 ≤ 100 个/ μ L。相较于AIDS/CM组,AIDS/CM/TBM组患者白细胞计数更高($P<0.05$),脑脊液蛋白含量更高($P<0.001$),而脑脊液糖水平更低($P<0.05$)。相较于AIDS/TBM组,AIDS/CM/TBM组患者脑脊液压力更高($P<0.001$),脑脊液氯化物水平更高($P<0.001$,表2)。

头颅MRI影像表现 39例AIDS/CM/TBM

患者中,34例(87.2%)颅内存在病灶,主要影像学表现为:(1)病灶分布。23例患者为多发病灶,11例患者为单发病灶。额叶、顶叶最为常见,11例患者存在基底节区域受累,其余部位包括颞叶、枕叶、小脑和脑膜。(2)病灶形态及MRI信号特点,主要分为脑膜炎型和脑膜脑炎型。①脑膜炎型表现为软脑膜增厚,形态欠光整,邻近脑实质可出见炎性水肿,增强后脑膜呈线样、条样强化,主要位于大脑凸面与小脑背面(图1);②脑膜脑炎型主要表现为血管周

表2 3组患者实验室检查结果比较

Tab 2 Comparison of laboratory tests among the three groups

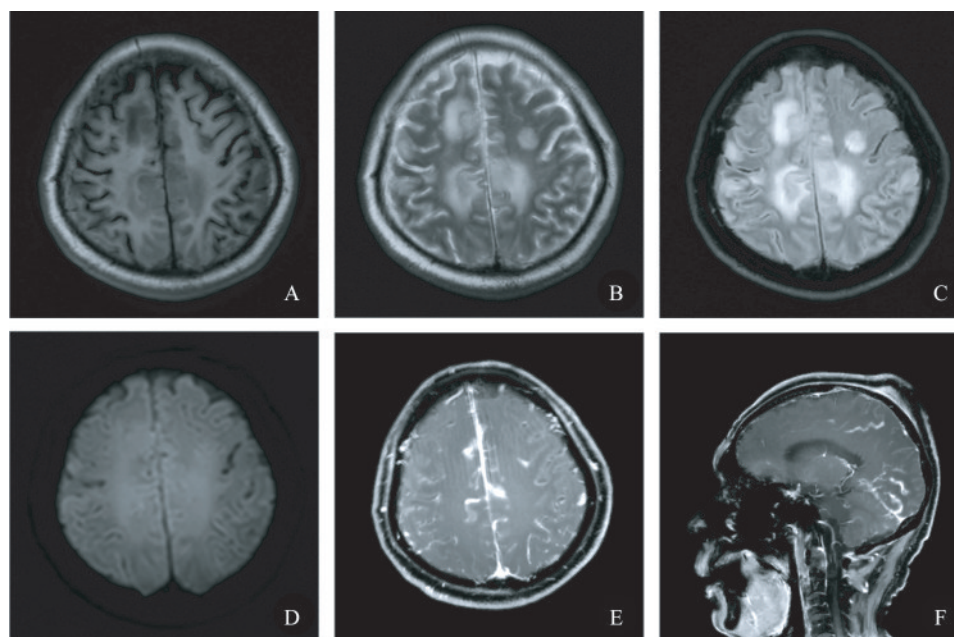
Laboratory tests	AIDS/CM/TBM	AIDS/CM	AIDS/TBM	Statistic	P
CD4+ T cell counts (/μL)	32.00 (15.00,80.00)	24.00 (12.50,54.00) ⁽²⁾	45.00 (20.75,122.00)	$\chi^2=7.231$	0.027
<50	24 (61.5)	43 (70.5)	22 (52.4)		
50-<100	8 (20.5)	13 (21.3)	7 (16.8)		
100-<200	3 (7.7)	4 (6.6)	11 (26.2)		
≥200	4 (10.3)	1 (1.6)	2 (4.8)		
White blood cell counts (/μL)	22.00 (10.00,82.00) ⁽¹⁾	10.00 (3.00,35.00)	20.00 (4.00,93.25)	$\chi^2=7.846$	0.020
CSF opening pressure (mmH ₂ O)	250.00 (160.00,300.00) ⁽²⁾	300.00 (192.50,350.00) ⁽²⁾	160.00 (118.75,220.00)	$\chi^2=27.865$	<0.001
CSF protein (mg/L)	1231.60 (862.90,1914.00) ⁽¹⁾	487.50 (286.00,764.35) ⁽²⁾	901.85 (481.55,2626.33)	$\chi^2=34.646$	<0.001
CSF chloride (mmol/L)	117.88±3.83 ⁽²⁾	120.35±6.75 ⁽²⁾	113.95±9.84	$F=10.876$	<0.001
CSF glucose (mmol/L)	1.94±0.75 ⁽¹⁾	2.55±0.88 ⁽²⁾	2.09±0.94	$F=7.038$	0.001

CSF: Cerebrospinal fluid. ⁽¹⁾vs. AIDS/CM group, $P<0.05$; ⁽²⁾vs. AIDS/TBM group, $P<0.05$. The measurement data subject to normal distribution are represented by $\bar{x}\pm s$. The measurement data not subject to normal distribution are represented by $M(P_{25}, P_{75})$. The enumeration data are represented by $n(\%)$.

围间隙(virchow-robin spaces, VRS)扩大或胶样假囊形成,多位于基底节区,呈对称性分布,T1WI呈低信号,T2WI、FLAIR呈稍高或高信号,DWI部分病灶扩散受限,增强后少数可见点状、絮片状强化(图2),与AIDS/CM组患者特征性表现相符。此外,无患者出现AIDS/TBM特征性表现,即结核

瘤,差异均有统计学意义($P<0.001$,表3)。(3)并发症:可出现脑积水、脑梗死,3组间差异无统计学意义(表3)。

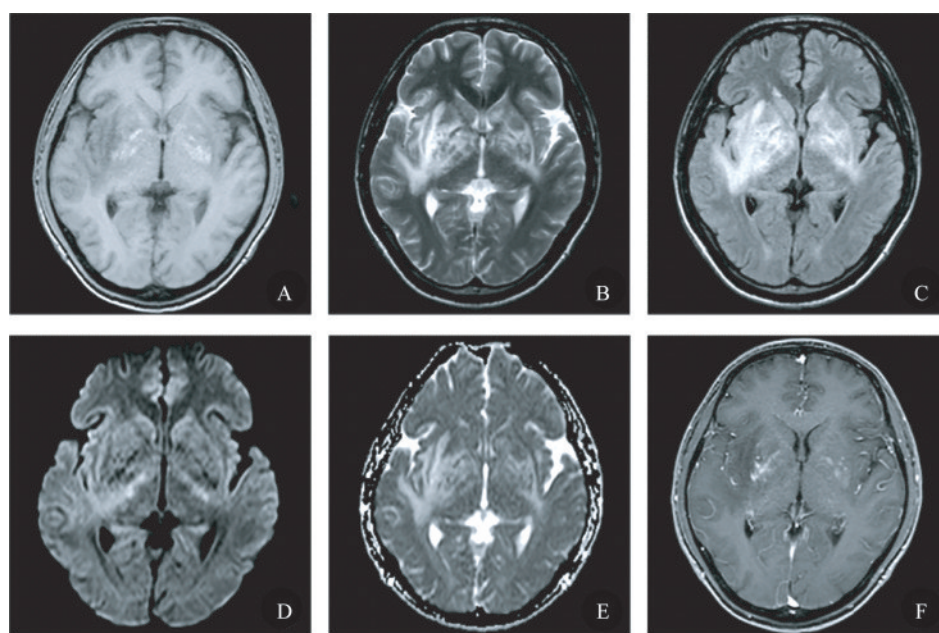
多因素 Logistic 回归分析 多因素回归分析结果显示,头痛、意识障碍及脑脊液糖 ≤ 1.85 mmol/L与AIDS/CM/TBM患者多重感染相关(表4)。



The meninges of the bilateral frontal-parietal area were thickened, with isointense on T1WI, T2WI, FLAIR, and large edema in adjacent to brain parenchyma (A-C), DWI showed no restriction (D), after contract, linear and strip-like enhancement were seen (E, F).

图1 脑膜炎型AIDS/CM/TBM患者的MRI表现

Fig 1 The MRI characteristics of meningitis in AIDS/CM/TBM patients



Large abnormal signals were seen in the bilateral basal ganglia regions, with hypointense on T1WI (A), hyper- or hypointense on T2WI and FLAIR (B, C), DWI and ADC showed partial restriction (D, E), after contract, dot and patchy enhancement were seen (F), and cerebral infarction in the bilateral basal ganglia regions with microbleeds.

图2 脑膜脑炎型 AIDS/CM/TBM 患者的 MRI 表现

Fig 2 The MRI characteristics of meningoencephalitis in AIDS/CM/TBM patients

表3 3组患者头颅MRI影像特征比较

Tab 3 Comparison of brain MRI characteristics among the three groups

[n(%)]

MRI characteristics	AIDS/CM/TBM	AIDS/CM	AIDS/TBM	χ^2	P
With intracranial lesions	34 (87.2)	45 (73.8)	34 (81.0)	2.701	0.250
With multiple lesions	23 (59.0)	29 (47.5)	20 (47.6)	1.471	0.491
Lesions distribution					
Basal ganglia region	11 (28.2) ⁽¹⁾⁽²⁾	23 (37.7) ⁽²⁾	6 (14.3)	6.742	0.033
Frontal lobe	17 (43.6) ⁽¹⁾⁽²⁾	10 (16.4) ⁽²⁾	10 (23.8)	9.289	0.010
Parietal lobe	18 (46.2) ⁽¹⁾	6 (9.8) ⁽²⁾	13 (31.0)	17.028	<0.001
Temporal lobe	11 (28.2) ⁽¹⁾	4 (6.6) ⁽²⁾	14 (33.3)	12.977	0.001
Occipital lobe	8 (20.5)	5 (8.2)	8 (19.0)	3.722	0.172
Cerebellum	7 (17.9)	5 (8.2)	8 (19.0)	3.084	0.218
Brainstem	0 (0.0)	2 (3.3)	3 (7.1)	Fisher exact probability	0.275
Lesions form					
Meningeal enhancement	10 (25.6)	6 (9.8)	8 (19.0)	4.427	0.115
Tuberculoma	0 (0) ⁽²⁾	0 (0) ⁽²⁾	10 (23.8)	Fisher exact probability	<0.001
Dilated VRS or pseudocyst	11 (28.2) ⁽²⁾	22 (36.1) ⁽²⁾	0 (0)	18.880	<0.001
Complication					
Cerebral infarction	14 (33.3)	17 (27.9)	14 (33.3)	0.635	0.730
Hydrocephalus	6 (15.4)	2 (3.3)	5 (11.9)	Fisher exact probability	0.083

VRS: Virchow-Robin spaces. ⁽¹⁾Compared with AIDS/CM group, $P<0.05$; ⁽²⁾Compared with AIDS/TBM group, $P<0.05$.

表4 艾滋病合并隐球菌性与结核性脑膜炎多重感染的多因素 Logistic 回归分析

Tab 4 Multivariate Logistic regression analysis for AIDS patients with cryptococcal meningitis and tuberculous meningitis co-infection

Factor	Cut-off value	OR	95% CI	P
Headache	-	9.112	1.740-47.721	0.009
Consciousness disorders	-	27.780	2.707-285.140	0.005
CSF glucose (mmol/L)	≤1.85	9.507	2.269-39.839	0.002

讨 论

传染性疾病多重感染是目前备受国内外关注的严重感染问题。CM和TBM作为高致死性中枢神经系统感染性疾病,是最常见的合并感染形式,在获得性免疫缺陷人群中,其感染风险明显增高^[6,10]。由于现有的结核病诊断分析方法在AIDS患者中的敏感性和特异性较低,导致合并结核病常被漏诊。本研究对比分析了AIDS/CM/TBM患者、AIDS/CM患者及AIDS/TBM患者的临床资料,结果显示AIDS/CM/TBM多重感染患者往往比AIDS/CM、AIDS/TBM合并感染患者出现更严重的临床症状,实验室检查各项检查指标变化也更显著,头颅MRI检查的阳性率更高,综合分析有助于早期诊断。

中枢神经系统感染的临床症状以头痛、发热为主,病情进展可出现精神和神经症状,或合并脑神经损伤,表现复杂但不具有特异性,容易造成误诊和漏诊。本研究结果显示AIDS/CM/TBM组患者抽搐、视力障碍和意识障碍的发生率明显高于其他两组患者,头痛的发生率则高于AIDS/TBM组。抽搐、意识障碍提示脑实质及功能受损,均可作为AIDS/CM患者预后判断和疗效评价的关键指标^[11],同时应警惕其提示合并TBM多重感染的可能性。头痛、视力障碍则与颅高压相关。颅内结核感染产生炎性渗出物^[12]与隐球菌的菌体聚集及荚膜多糖^[13]都会使脑脊液重吸收障碍,进一步导致颅内压升高,多重感染时更容易出现顽固性颅高压。本研究多因素回归分析结果进一步显示,头痛与意识障碍有助于提示合并多重感染。

实验室检查中,CD4⁺T淋巴细胞计数水平可用于评估AIDS患者机会性感染的风险。CD4⁺T淋

巴细胞计数≤100个/μL时,TBM多见;≤50个/μL时,CM、弓形虫脑病及原因不明感染多见^[14]。本研究39例AIDS/CM/TBM患者中,32例(82.0%)CD4⁺T淋巴细胞计数≤100个/μL,提示重度免疫抑制。结合前期病例报道^[15-18],可推论病毒高复制状态和免疫功能严重缺陷是AIDS患者发生TBM和CM感染的重要原因,当CD4⁺T淋巴细胞计数≤100个/μL时,应警惕TBM和CM合并感染的可能性。脑脊液生化检查对中枢神经系统感染具有一定的诊断价值。《艾滋病合并隐球菌病临床诊疗的专家共识》指出AIDS/CM患者脑脊液蛋白质水平多呈轻至中度升高,葡萄糖和氯化物水平下降,有结核杆菌多重感染时可出现蛋白质水平明显增高^[4],本研究结果与其相符。既往研究提出,脑脊液压力联合葡萄糖、蛋白质和氯化物水平可作为合并感染有效的鉴别标志物(AUC=0.89)。本研究单因素分析显示,对比AIDS/CM与AIDS/TBM双重感染组,AIDS/CM/TBM组患者的各项生化检查指标均更为显著。而多因素回归结果表明,脑脊液糖≤1.85 mmol/L与AIDS/CM/TBM多重感染相关,可能是由于多重感染造成更为严重的血脑屏障破坏及血浆中糖代谢紊乱、转运障碍,导致脑脊液中糖水平的明显变化。

影像学表现方面,TBM和CM均可出现脑膜与脑实质病变,TBM主要表现为颅底脑池的脑膜强化及脑实质大小不等的结核灶^[19],CM则可出现特征性的基底节区VRS增宽及胶样假囊形成^[20]。本研究中,AIDS/CM/TBM患者总体符合CM影像学表现,以脑膜炎型和脑膜脑炎型为主,而病变更易累及大脑各脑叶。隐球菌菌体聚集在VRS,分泌胶冻样物质,使该区域空间明显增宽,并形成胶样假囊^[20],AIDS/CM/TBM患者VRS增宽及胶样假囊的发生率较低,可能与同时合并结核分支杆菌感染有关,但其多重感染的病理生理及相互作用机制尚未阐明,有待进一步探究。另AIDS/CM/TBM患者部分病灶存在强化,可能是由于感染引起巨噬细胞黏附迁移,导致微小血管完整性破坏,通透性增强,从而引起血管强化^[21]。

对于AIDS/CM/TBM患者而言,早期精准临床干预是取得良好预后的关键。有研究表明,结核病预防性治疗(tuberculosis preventive therapy, TPT)可以降低AIDS患者的结核病发病率,尤其是

晚期免疫抑制的危重 AIDS 患者^[22]。但是,在常规抗真菌治疗的背景下,TPT 的启动可能会引起复杂的药物相互作用^[22],并为患者增加用药负担。因此,TPT 的推广应用仍需一定规模的临床试验,例如短期 TPT 联合试验持续监测耐药性、相互作用和不良影响,以及进一步进行随机对照试验,评估其在晚期 AIDS 或合并 CM 患者治疗中的有效性和安全性。

目前,国内外研究多为颅内单一感染的鉴别诊断^[25-26],AIDS/CM/TBM 多重感染与 AIDS/CM、AIDS/TBM 双重感染的鉴别诊断目前未见报道,本研究综合临床表现、实验室检查及头颅影像学表现,全面分析可用于 AIDS/CM/TBM 早期准确诊断的线索,有助于提高临床医师对 AIDS 患者合并多种中枢神经系统感染的认识,更加科学客观地进行诊治。但本研究也存在一些局限性:(1)病例数相对较少,结果可能存在偏倚;(2)属于单中心回顾性研究,且无既往研究结果对比验证;(3)仅对鉴别诊断相关因素进行分析,未就治疗方案及长期疗效进行随访。因此,所得结论仍需扩大样本量、多中心及前瞻性研究进一步讨论。

综上所述,AIDS/CM/TBM 多重感染与 AIDS/CM 及 AIDS/TBM 双重感染的临床表现、实验室检查与头颅 MRI 表现虽有类似,但仍存在一定差异,临床医师应该提高对 AIDS 患者合并多种中枢神经系统感染的认识,尽可能实现早期诊断、精准治疗,最大程度改善患者预后。

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利益冲突声明 所有作者均声明不存在利益冲突。

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