·中枢神经系统感染性疾病·

耐药结核性脑膜炎动态脑脊液细胞学研究

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【摘要】 **目的**　总结耐药结核性脑膜炎的脑脊液细胞学动态变化特点，并探讨其在结核性脑膜炎耐药和疗效评估中的价值。**方法**　共纳入2013年1月至2020年12月在江西省胸科医院诊断与治疗的79例结核性脑膜炎患者，行脑脊液药敏检测和至少每周一次的脑脊液细胞学检查，计数有核细胞和各类细胞百分比；药敏检测结果回报前采取H(S)REZ(V)方案，结果回报后根据耐药情况制定个体化抗结核方案。**结果**　根据脑脊液药敏检测结果，37例为耐药结核性脑膜炎，其中29例(78.38%)为多药耐药，耐药谱依次为异烟肼+利福平+链霉素[35.14%(13/37)]，异烟肼+利福平+链霉素+氟喹诺酮[18.92%(7/37)]，异烟肼+利福平+乙胺丁醇+链霉素[16.22%(6/37)]，异烟肼和利福平[各10.81%(4/37)]，异烟肼+利福平、异烟肼+利福平+乙胺丁醇+链霉素+氟喹诺酮、异烟肼+利福平+乙胺丁醇+链霉素+阿米卡星/卷曲霉素[各2.70%(1/37)]。抗结核治疗2和4周后，非耐药组脑脊液有核细胞计数(t=5.050，P=0.000；t=11.100，P=0.000)和中性粒细胞比例(t=15.268，P=0.000；t=17.048，P=0.000)均低于耐药组。脑脊液细胞学显示，耐药组呈现持续>4周的混合细胞炎症迁延反应，非耐药组向显著淋巴细胞反应转化。随访6个月时，耐药组总有效率低于非耐药组[45.71%(16/35)对90%(36/40)；χ^2=17.218，P=0.000]。**结论**　结核性脑膜炎早期脑脊液细胞学以混合细胞炎症反应为主，治疗过程中持续>4周的混合细胞炎症迁延反应是耐药结核性脑膜炎的特点，可能是提示治疗方案无效的依据。临床受限于药敏检测时限和条件限制时，监测脑脊液细胞学动态变化可能成为耐药结核性脑膜炎的辅助判断方法，可为临床疗效评价和抗结核治疗方案调整提供参考。

【关键词】 结核，脑膜；　药物耐受性；　微生物敏感性试验；　脑脊髓液；　细胞学

Clinical study of dynamic changes of cerebrospinal fluid cytology in drug resistant tuberculous meningitis

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【**Abstract**】 **Objective**　To summarize the dynamic changes of cerebrospinal fluid (CSF) cytology in drug resistant tuberculous meningitis (TBM), and to explore its value in drug resistance and efficacy evaluation of TBM. **Methods**　Seventy-nine patients with TBM who were diagnosed and treated in Jiangxi Chest Hospital from January 2013 to December 2020 were included in this study. H(S)REZ(V) scheme [isoniazid (or streptomycin), rifampicin, ethambutol, plus pyrazinamide (or levofloxacin)] regimen was adopted before the return of drug sensitivity test results. After the return of results, individualized anti-tuberculosis regimen was formulated according to drug resistance. **Results**　According to the drug sensitivity test results of CSF, 37 cases were drug resistant TBM, of which 29 cases (78.38%) were multidrug resistant. The drug resistance spectrum was isoniazid + rifampicin + streptomycin [35.14% (13/37)], isoniazid + rifampicin + streptomycin + fluoroquinolone [18.92% (7/37)], isoniazid + rifampicin + ethambutol + streptomycin [16.22% (6/37)], isoniazid and rifampicin [10.81% each, (4/37)], Isoniazid + rifampicin, isoniazid + rifampicin + ethambutol + streptomycin + fluoroquinolone, isoniazid + rifampicin + ethambutol +

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streptomycin + amikacin/capreomycin [2.70% each, (1/37)]. After 2 and 4 weeks of antituberculosis treatment, the number of nucleated cells in CSF of non drug resistant group (t = 5.050, P = 0.000; t = 11.100, P = 0.000) and neutrophil ratio (t = 15.268, P = 0.000; t = 17.048, P = 0.000) were lower than drug resistant group. CSF cytology showed that the drug resistant group showed mixed cell inflammatory reaction lasting more than 4 weeks, and the non drug resistant group transformed into significant lymphocyte reaction. After 6 months of follow-up, the total effective rate of drug resistant group was lower than that of non drug resistant group [45.71% (16/35) vs. 90% (36/40); χ^2 = 17.218, P = 0.000]. **Conclusions** The cytological characteristics of CSF in patients with TBM are mainly characterized by mixed cell inflammatory reaction in the early stage, the delayed mixed cell inflammatory reaction lasting more than 4 weeks during treatment is the characteristic of drug resistant TBM, which may be the basis for indicating that the treatment plan is invalid. When limited by the time limit and conditions of drug sensitivity test, monitoring the dynamic changes of CSF cytology may become an auxiliary judgment method for drug resistant TBM, which can provide reference for clinical efficacy evaluation and antituberculosis treatment plan adjustment.

【Key words】 Tuberculosis, meningeal; Drug tolerance; Microbial sensitivity tests; Cerebrospinal fluid; Cytological techniques

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结核病是严重危害人类健康的全球性公共卫生问题。结核性脑膜炎(TBM)是最严重的肺外结核病,病死率和病残率高达45%[1]。随着我国结核病治疗中获得性耐药菌株的不断增多,耐药结核性脑膜炎日益受到关注,其诊断与治疗愈加困难。脑脊液细胞学及其动态变化可以在一定程度上反映蛛网膜下腔炎症状态,对中枢神经系统感染的诊断与鉴别诊断有重要辅助价值[2]。本研究回顾性总结37例耐药结核性脑膜炎患者的脑脊液细胞学动态变化特点,以期探讨该项技术对结核性脑膜炎耐药和疗效评估的价值。

资料与方法

一、临床资料

1. 纳入标准 (1)结核性脑膜炎的诊断符合Marais等[2]的标准。(2)脑脊液检出结核分枝杆菌表型或基因型证据,且有培养和(或)基于核酸的药敏快速检测结果。(3)治疗开始后至少每周进行一次脑脊液细胞学检查,连续不少于4周。

2. 排除标准 (1)治疗4周内因并发症终止药物治疗。(2)因颅内高压或脑积水行脑室外引流术或腰大池引流术。(3)脑实质占位性病变致脑疝。

3. 一般资料 根据上述纳入与排除标准,选择2013年1月至2020年12月在江西省胸科医院神经内科住院治疗的结核性脑膜炎患者共79例,其中男性47例,女性32例;年龄10~78岁,中位年龄37(21,49)岁;发病至确诊时间3~82 d,平均(21.30±10.16) d;临床主要表现为头痛占100%(79/79),发热占100%(79/79),脑膜刺激征占92.41%(73/79)。首次腰椎穿刺脑脊液检查压力为95~350 mm H_2O(1 mm H_2O = 9.81 × 10^{-3} kPa),平均为(167.35±61.83) mm H_2O;有核细胞计数(76~421)×10^6/L,平均为(159.21±56.25)×10^6/L;蛋白定量为825~2389 mg/L,平均(1125.71±126.69) mg/L;葡萄糖0.47~4.52 mmol/L,平均(1.45±0.67) mmol/L;氯化物106~127 mmol/L,平均(112.34±13.53) mmol/L。

二、研究方法

1. 治疗方法 (1)抗结核治疗:所有患者均于临床诊断或确诊后接受抗结核治疗,脑脊液药敏检测结果回报前采取H(S)REZ(V)方案,即异烟肼(H)0.60 g/d+链霉素(S)0.75 g/d+利福平(R)0.45 g/d+乙胺丁醇(E)0.75 g/d+吡嗪酰胺(Z)1.50 g/d+左氧氟沙星(V)0.60 g/d;药敏检测结果回报后,根据耐药情况制定个体化抗结核方案,包含未应用过的药物和3种敏感药物共4~5种药物[3],根据治疗效果,总疗程持续2~3年。(2)脱水降低颅内压和糖皮质激素治疗:予以20%甘露醇、10%甘油果糖、白蛋白和呋塞米(速尿)静脉滴注或者静脉注射减轻脑水肿,以及地塞米松用于抑制炎症反应,初始剂量为10~15 mg/d,并根据病情恢复情况减量、停药,总疗程持续4~8周[4]。

2. 脑脊液药敏检测 所有患者均于首次腰椎穿刺收集脑脊液4 ml,采用以下至少1种方法行结核分枝杆菌药敏检测:改良罗氏结核分枝杆菌培养、

BACTEC-MGIT960结核分枝杆菌快速培养、荧光定量聚合酶链反应(FQ-PCR)溶解曲线核酸检测、反相杂交核酸检测、结核分枝杆菌及利福平快速耐药检测(Xpert MTB/RIF)[5-6]。以药敏检测结果呈阳性判断为耐药结核性脑膜炎。

3.脑脊液细胞学检测 所有患者治疗开始后至少每周进行一次脑脊液细胞学检查,每次收集脑脊液0.50~2.00 ml,采用空军军医大学西京医院自行研制的FMU-6型脑脊液细胞玻片离心沉淀器收集脑脊液细胞,采用黏附玻片,离心半径140 mm、转速600 r/min离心5 min,自动制备细胞玻片,行迈-格-姬(MGG)染色8 min,于光学显微镜(×100)下连续计数不少于3个视野细胞,根据MGG染色胞核形态[7]进行细胞分类并计算各类细胞百分比。

4.疗效评价 治疗后随访6个月,根据临床症状与体征、脑脊液细胞学和影像学检查结果评价临床疗效[4,7],有效,临床症状与体征好转,影像学显示脑膜强化、脑实质病灶和脑积水好转,脑脊液常规和生化指标显著好转或接近正常水平,有或无神经损害后遗症;无效,临床症状与体征无好转,影像学无好转,脑脊液常规和生化指标无明显改善,甚至加重恶化或死亡。

5.统计分析方法 采用SPSS 20.0统计软件进行数据处理与分析。计数资料以相对数构成比(%)或率(%)表示,采用χ^2检验或Fisher确切概率法;呈正态分布的计量资料以均数±标准差($\bar{x}\pm s$)表示,采用两独立样本的t检验。以$P\leq0.05$为差异具有统计学意义。

结 果

根据脑脊液药敏检测结果,37例为耐药结核性脑膜炎(耐药组),42例为非耐药结核性脑膜炎(非耐药组);两组患者一般资料比较,差异无统计学意义(均$P>0.05$,表1)。37例耐药结核性脑膜炎患者中29例(78.38%)为多药耐药,耐药谱最多为异烟肼+利福平+链霉素(13例占35.14%),其次依次为异烟肼+利福平+链霉素+氟喹诺酮(7例占18.92%),异烟肼+利福平+乙胺丁醇+链霉素(6例占16.22%),异烟肼和利福平(各4例占10.81%),异烟肼+利福平、异烟肼+利福平+乙胺丁醇+链霉素+氟喹诺酮、异烟肼+利福平+乙胺丁醇+链霉素+阿米卡星/卷曲霉素(各1例占2.70%,表2);其中21例(56.76%)予一线抗结核药物治疗4周后获得脑脊液耐药证据而调整治疗方案。

表1 耐药组与非耐药组患者临床资料的比较

Table 1. Comparison of clinical data between drug resistant group and non drug resistant group

项目	耐药组(n=37)	非耐药组(n=42)	χ^2或t值	P值
性别[例(%)]			0.032	0.859
男性	21(56.76)	23(54.76)		
女性	16(43.24)	19(45.24)		
年龄($\bar{x}\pm s$,岁)	36.63± 11.22	37.95± 12.36	0.488	0.626
发病至确诊时间($\bar{x}\pm s$,d)	22.10± 11.32	20.90± 9.96	0.501	0.618
临床表现[例(%)]				
头痛	37(100.00)	42(100.00)	—	—
发热	37(100.00)	42(100.00)	—	—
脑膜刺激征	34(91.89)	39(92.86)	0.000	1.000
脑脊液检查($\bar{x}\pm s$)				
压力(mm H_2O)	172.06± 69.53	159.72± 64.56	0.812	0.416
有核细胞计数(×10^6/L)	175.65± 56.28	169.55± 52.37	0.499	0.619
蛋白定量(mg/L)	1125.21±113.62	1156.41±121.13	1.176	0.243
葡萄糖(mmol/L)	1.39± 0.92	1.45± 0.56	0.355	0.724
氯化物(mmol/L)	112.23± 15.30	115.91± 12.27	1.185	0.240

—, no data, 无数据。χ^2 test for comparison of sex, headache and fever, adjusted χ^2 test for comparison of meningeal irritation, and two-independent-sample t test for comparison of others, 性别、头痛、发热的比较行χ^2检验,脑膜刺激征的比较行校正χ^2检验,其余各项比较行两独立样本的t检验

治疗前,耐药组与非耐药组患者脑脊液有核细胞计数和细胞学转化分类差异均无统计学意义($P>0.05$,表3);抗结核治疗2周后,非耐药组脑脊液有核细胞计数($P=0.000$)和中性粒细胞比例($P=0.000$)均低于耐药组,淋巴细胞($P=0.007$)、激活淋巴细胞($P=0.000$)、单核细胞($P=0.000$)、激活单核细胞($P=0.000$)和浆细胞($P=0.000$)比例均高于耐药组(表4);抗结核治疗4周后,非耐药组脑脊液有核细胞计数($P=0.000$)和中性粒细胞比例($P=0.000$)亦低于耐药组,激活淋巴细胞($P=0.000$)、单核细胞($P=0.010$)、激活单核细胞($P=0.000$)和浆细胞($P=0.012$)比例均高于耐药组(表5)。脑脊液细胞学显示,所有患者治疗前均呈现混合细胞反应(图1)。耐药组抗结核治疗4周后,33例表现为持续超过4周的混合细胞炎症迁延反应(图2),即使根据药敏检测结果更改治疗方案,仅9例向显著淋巴细胞反应转化,提示治疗有效;其余4例脑脊液细胞学好转者均为单药耐药患者。非耐药组抗结核治

表2 37例耐药结核性脑膜炎患者的耐药谱[例(%)]

Table 2. Drug resistance spectrum of 37 patients with drug resistant TBM [case (%)]

耐药谱	耐药病例数	耐药谱	耐药病例数
异烟肼	4(10.81)	异烟肼+利福平+乙胺丁醇+链霉素	6(16.22)
异烟肼+利福平	1(2.70)	异烟肼+利福平+链霉素+氟喹诺酮	7(18.92)
利福平(Xpert MTB/RIF)	4(10.81)	异烟肼+利福平+乙胺丁醇+链霉素+氟喹诺酮	1(2.70)
异烟肼+利福平+链霉素	13(35.14)	异烟肼+利福平+乙胺丁醇+链霉素+阿米卡星/卷曲霉素	1(2.70)

Xpert MTB/RIF, rapid detection of Mycobacterium tuberculosis and rifampicin resistance by semi-nested time PCR, 半巢式全自动实时荧光定量聚合酶链反应结核分枝杆菌及利福平快速耐药检测

表3 耐药组与非耐药组患者治疗前脑脊液有核细胞计数和各类细胞百分比的比较($\bar{x} \pm s$)

Table 3. Comparison of nucleated cell count and cytological transformation classification of cerebrospinal fluid between drug resistant group and non drug resistant group before treatment ($\bar{x} \pm s$)

组别	有核细胞计数($\times 10^6$/L)	各类细胞百分比(%)				
		中性粒细胞	淋巴细胞	激活淋巴细胞	单核细胞	激活单核细胞
耐药组	172.06±69.52	58.27±8.52	2.70±0.21	28.11±3.55	1.31±0.06	9.16±1.05
非耐药组	159.75±64.51	61.73±9.34	2.56±0.45	26.92±4.13	1.24±0.21	8.85±1.45
t值	0.816	1.533	1.730	1.364	1.957	1.075
P值	0.417	0.130	0.087	0.177	0.054	0.286

表4 耐药组与非耐药组患者治疗后2周脑脊液有核细胞计数和各类细胞百分比的比较($\bar{x} \pm s$)

Table 4. Comparison of nucleated cell count and cytological transformation classification in cerebrospinal fluid between drug resistant group and non drug resistant group 2 weeks after treatment ($\bar{x} \pm s$)

组别	有核细胞计数($\times 10^6$/L)	各类细胞百分比(%)					
		中性粒细胞	淋巴细胞	激活淋巴细胞	单核细胞	激活单核细胞	浆细胞
耐药组	159.83±63.18	51.21±7.62	8.14±2.33	30.08±5.11	1.12±0.26	8.17±1.22	1.28±0.12
非耐药组	103.71±32.53	26.82±6.58	9.57±2.28	38.93±5.65	2.28±0.55	20.31±3.26	2.09±0.25
t值	5.050	15.268	2.753	7.263	11.721	21.359	17.960
P值	0.000	0.000	0.007	0.000	0.000	0.000	0.000

表5 耐药组与非耐药组患者治疗后4周脑脊液有核细胞计数和各类细胞百分比的比较($\bar{x} \pm s$)

Table 5. Comparison of nucleated cell count and cytological transformation classification in cerebrospinal fluid between drug resistant group and non drug resistant group 4 weeks after treatment ($\bar{x} \pm s$)

组别	有核细胞计数($\times 10^6$/L)	各类细胞百分比(%)					
		中性粒细胞	淋巴细胞	激活淋巴细胞	单核细胞	激活单核细胞	浆细胞
耐药组	161.64±61.22	25.23±8.58	2.46±0.22	59.13±9.21	0.58±0.05	10.14±2.25	2.46±0.62
非耐药组	49.71±21.63	2.66±0.34	2.58±0.36	85.92±5.35	0.54±0.08	6.18±2.54	2.12±0.56
t值	11.100	17.048	1.758	16.036	2.622	7.291	2.561
P值	0.000	0.000	0.083	0.000	0.010	0.000	0.012

疗2周后中性粒细胞比例有一定程度下降(图3),治疗4周后有38例向显著淋巴细胞反应转化(图4)。

治疗后随访6个月,耐药组37例患者中16有效、19例无效(其中17例死亡,多药耐药患者占16/17例)、2例未完成随访,总有效率为45.71%(16/35);非耐药组42例患者中36例有效、4例无效(其中3例死亡)、2例未完成随访,总有效率为90%(36/40)。两组患者治疗总有效率差异有统计学意义($\chi^2 = 17.218$, $P = 0.000$)。脑脊液细胞学显示,治疗无效者始终呈现持续混合细胞反应。

讨 论

耐药性结核病是许多国家新出现的卫生健康问题,尤其是多药耐药结核病(MDR-TB)是我国结核病控制工作中面临的严峻挑战。随着结核分枝杆菌耐药菌株的增多[8-9],耐药结核性脑膜炎发病率

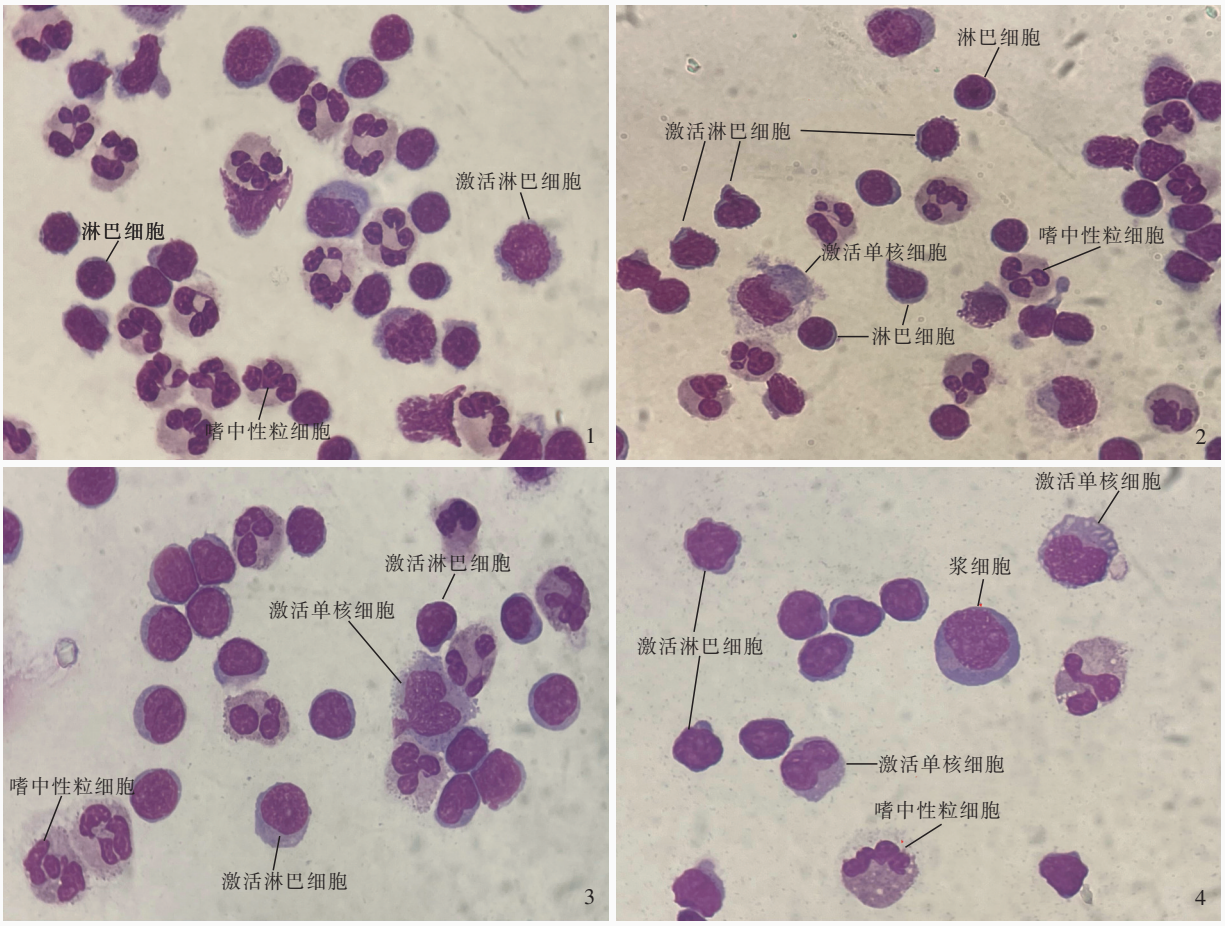

图1　结核性脑膜炎患者治疗前脑脊液细胞学显示，分叶核细胞与单叶核细胞混合存在，且比例接近　**图2**　耐药结核性脑膜炎患者治疗4周后脑脊液细胞学显示，分叶核细胞与单叶核细胞混合存在，且比例接近，并未向淋巴细胞转化　**图3**　非耐药结核性脑膜炎患者治疗2周后脑脊液细胞学显示，分叶核细胞与单叶核细胞混合存在，但分叶核细胞比例有所减少　**图4**　非耐药结核性脑膜炎患者治疗4周后脑脊液细胞学显示，有核细胞数目减少，分叶核细胞比例明显下降，向淋巴细胞转化

Figure 1　Cerebrospinal fluid (CSF) cytology before treatment in patients with tuberculous meningitis (TBM) showed a mixture of lobulated and unilobulated nuclear cells in a similar proportion.　**Figure 2**　CSF cytology from a patient with drug resistant TBM after 4 weeks of treatment showed a mixture of lobulated and unilobulated nuclear cells in a similar proportion and no transformation to lymphocytes.　**Figure 3**　CSF cytology from patients with non drug resistant TBM after 2 weeks of treatment showed a mixture of lobulated and unilobulated nuclear cells, but a reduced proportion of lobulated nuclear cells.　**Figure 4**　CSF cytology from a patient with non drug resistant TBM after 4 weeks of treatment showed a decrease in the number of nucleated cells in the field of vision, and a significant decrease in the proportion of lobulated nucleated cells, transforming into lymphocytes.

和病死率逐年增加[10-11]。耐药结核性脑膜炎的临床特征、神经影像学、病理学和脑脊液细胞学早期特征均与药物敏感结核性脑膜炎相似[12-13]。结核性脑膜炎脑脊液结核分枝杆菌含量较少，临床病原菌阳性检出率低，尽管分子诊断技术的迅速发展为病原诊断提供了有效补充手段，但仍未大幅度提高病原菌阳性检出率，且其阳性检出率受方法学的影响，尤其在脑脊液结核分枝杆菌耐药检测方面，技术难以普及，漏检率较高[14-16]。本研究根据脑脊液药敏检测结果，37例为耐药结核性脑膜炎，其中29例（78.38%）为多药耐药，其耐药谱依次为异烟肼+利福平+链霉素[35.14%（13/37）]，异烟肼+利福平+链霉素+氟喹诺酮[18.92%（7/37）]，异烟肼+利福平+乙胺丁醇+链霉素[16.22%（6/37）]，异烟肼和利福平[各10.81%（4/37）]，异烟肼+利福平、异烟肼+利福平+乙胺丁醇+链霉素+氟喹诺酮、异烟肼+利福平+乙胺丁醇+链霉素+阿米卡星/卷曲霉素[各2.70%（1/37）]。

脑脊液细胞学检查通过细胞分类以详细评估脑脊液炎症和免疫反应状态。耐药结核性脑膜炎的脑脊液细胞学与药物敏感结核性脑膜炎一样，早期均以混合细胞反应为主，部分严重患者中性粒细胞比例>60%，应注意与化脓性脑膜炎相鉴别[17-18]。嗜中性粒细胞比例增加是严重感染的标记，随着病

情进展，嗜中性粒细胞、淋巴细胞、转化型淋巴细胞、单核细胞并存，各类细胞百分比相近，呈典型混合细胞反应。有学者提出，嗜中性粒细胞比例显著降低（<10%）提示病情显著改善[19]。耐药结核性脑膜炎由于初始抗结核治疗效果较差，导致病情迁延，无法有效控制脑脊液炎症反应，其细胞学表现为长时间的混合细胞反应[20]。在本研究中，抗结核治疗2和4周后，非耐药组脑脊液有核细胞计数和中性粒细胞比例均低于耐药组；而且，由于疾病早期未获得药敏检测结果，致使耐药组脑脊液细胞学呈现持续>4周的混合细胞炎症迁延反应，可能为治疗方案无效的依据，而非耐药组抗结核治疗4周内脑脊液有核细胞计数显著下降，细胞学向显著淋巴细胞反应转化，提示治疗方案有效。

综上所述，临床受限于药敏检测时限和条件的限制时，监测脑脊液细胞学动态变化可能成为耐药结核性脑膜炎的辅助判断方法，可以为临床疗效评价和抗结核治疗方案调整提供参考。

利益冲突 无

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