· 论　　著 ·

鞘内注射两性霉素 B 联合静脉滴注伏立康唑成功救治 1 例脑曲霉菌病患者

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[摘要] **目的**　脑曲霉菌病的发病率日益增多,治疗药物有限,病死率很高。总结成功救治 1 例脑曲霉菌病患者的经验。**方法**　立体定向下行脑穿刺活检术,脑组织病理活检结果明确诊断。治疗采用联合抗真菌治疗,伏立康唑 0.2 g,2/d,静脉滴注,疗程 70 d;间断小剂量鞘内注射两性霉素 B,剂量 0.1 mg,1/周。**结果**　复查头颅磁共振,与初起病时比较病变明显吸收,临床症状好转。随访 3 年无复发。**结论**　小剂量两性霉素 B 鞘内注射联合静脉滴注伏立康唑治疗脑曲霉菌病有较好疗效,无明显不良反应。

[关键词]　鞘内注射;两性霉素 B;伏立康唑;脑曲霉菌病

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Successful treatment of cerebral aspergillosis with intrathecal injection amphotericin B and intravenous voriconazole

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[**Abstract**]　**Objective**　Cerebral aspergillosis is increasing with more immunocompromised hosts. At present, the treatment of cerebral aspergillosis is limited, which has a high mortality rate. We treated of a cerebral aspergillosis patient successfully, and provided the clinical reference. **Methods**　We reported a case of a cerebral aspergillosis who was diagnosed by brain biopsy. We therapy with intravenous caspofungin by two 0.2 g dose/day for 70 days, and combined intermittent small doses of intrathecal injection of amphotericin B by dose of just 0.1 mg, 1/week. **Results**　A magnetic resonance imaging of the brain and a cranial CT scan were reviewed. Pathological changes were absorbed and clinical symptoms from the previous improved markedly. We reviewed follow-up of 3 years without recurrence. **Conclusion**　Therapy with intravenous caspofungin and combined intermittent small doses of intrathecal injection of amphotericin B has a effect therapy, and which has a low side effect.

[**Key words**]　intrathecal injection; amphotericin B; voriconazole; cerebral aspergillosis

曲霉菌病多发生于肺部,在中枢神经系统发病率较低(10% ~20%)[1],常见于免疫功能低下及长期使用糖皮质激素的患者[2]。即使采取积极治疗措施,脑曲霉菌病的病死率仍然较高[3]。免疫缺陷的患者病死率甚至高达 99%[4]。早期检查并正确的诊断对于治疗脑曲霉菌病至关重要。目前两性霉素 B 仍然是治疗此病的一线药物[5],但是两性霉素 B 存在剂量相关的毒副作用,限制了其临床应用[5-6]。我们用小剂量两性霉素 B 鞘内注射联合静脉滴注伏立康唑,成功救治了 1 例脑曲霉菌病患者。

1　对象与方法

1.1　*病历资料*　患者男性,33 岁。因反复言语混乱 18 d 于 2011 年 5 月 1 日入院。既往身体健康,否认有呼吸及循环系统疾病病史。发病前 1 个月余出现反应迟钝、言语错乱,轻度躁狂,外院按“精神障碍”对症治疗效果不良而转诊我院。主要阳性体征:烦躁不安,表情呆滞,反应迟钝,动作缓慢,智力减退,言语错乱。血液检查生化、电解质、凝血因子、尿及粪常规无明显异常。血常规:WBC 9.9×10^9/L,N 81.90%,L 13.29%。抗“O”、类风湿因子阴性,C 反应蛋白 31.5 mg/L。乙型肝炎、艾滋病、梅毒相关检查均为阴性。腰穿颅压正常,脑脊液常规、生化、免疫球蛋白大致正常,未见结核杆菌、隐球菌、霉菌及其他细菌生长。胸部 CT 大致正常。头颅 MRI 示双侧脑白质可见片状囊状长 T1 长 T2 信号影,以双侧脑室旁为多,边界不清,FLAIR 像呈高信号,DWI 呈片状高信号及环状高信号影,ADC 呈片状低信号及囊性高信号影,增强扫描呈明显强化表现。囊性病灶呈环形强化表现(图 1)。入院后 1 周

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行立体定向下穿刺活检,病理报告:送检脑组织(右侧脑室前角病灶穿刺组织)炎性改变伴胶质细胞变性,结合特染考虑真菌感染(曲霉菌病)(图 2)。

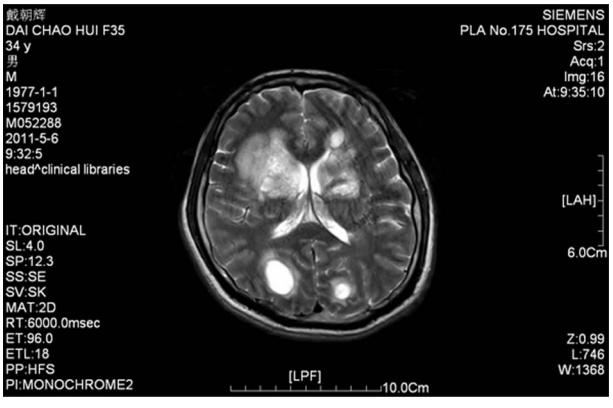
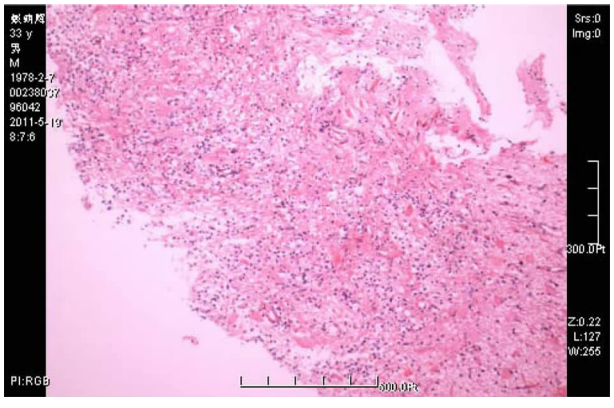
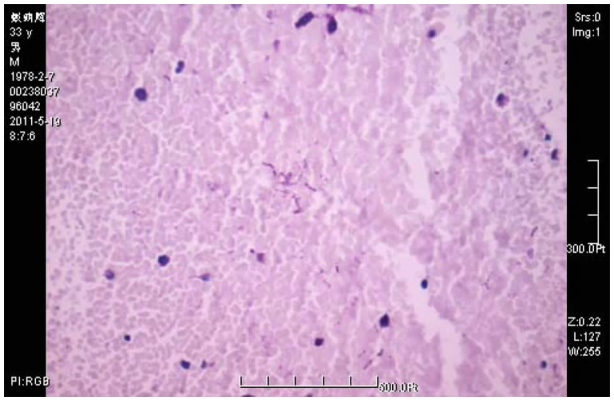


图 1　头颅磁共振 T2 加权像:颅内多发囊性病变



a



b

图 2　右侧脑室前角病灶穿刺组织病理报告(a:HE ×100;b:HE ×400)

1.2 *治疗方法*　伏立康唑 0.2 g,2/d,静脉滴注连续 70 d。间断腰穿鞘内注射 5% 葡萄糖 8 mL,两性霉素 B 0.1 mg,地塞米松 5 mg,1/周,共 4 周。辅助应用甘露醇脱水,维持水电解质平衡,保肝、降温等对症治疗及丹参川芎嗪注射液活血。

1.3 *并发症和不良反应*　腰穿鞘内注射两性霉素 B 后患者多次出现发热,最高体温 38.0 ℃,给予物理降温后热退。曾出现排尿困难症状,暂停鞘内注射导尿后症状逐渐缓解。

2　结　果

1 个月后患者智力明显改善,对答切题,行走平稳。复查头颅 MRI:颅内病变较前吸收减少。2 个月后复查颅脑 MRI 平扫 + 增强 + MRA:病变较前吸收。颅脑 MRA 符合动脉硬化。6 个月后(2012-01-17)复查头颅 MRI:病变较前吸收(图 3)。患者意识清楚,智力明显恢复,行走步态正常。随访 3 年无复发。2013 年 12 月复查头颅 MRI 示病变较前吸收(图 4)。

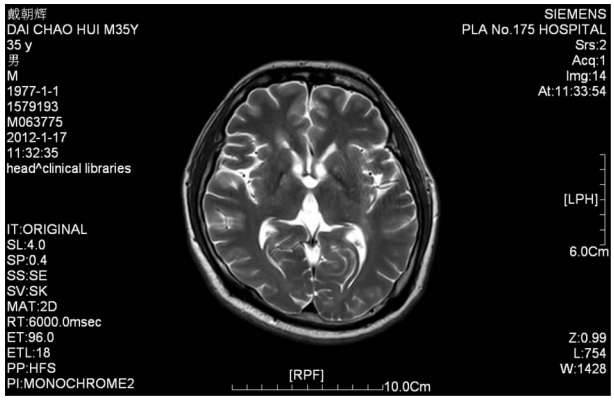


图 3　头颅磁共振 T2 加权像:颅内感染治疗 6 个月后复查颅内病灶较前吸收(2012-01)

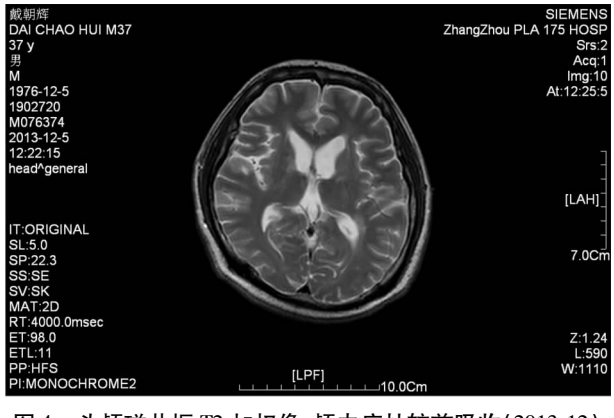


图 4　头颅磁共振 T2 加权像:颅内病灶较前吸收(2013-12)

3　讨　论

中枢神经系统真菌感染多为亚急性起病,病情表现多样,急性期炎性渗出明显。因病原体较大,毒力较低,易形成局限性化脓、肉芽肿或囊肿等。根据临床表现分为脑膜炎型、脑膜脑炎型、脑血管型

(血管炎引起脑血栓形成或脑出血,真菌性心内膜炎导致脑动脉栓塞)和颅内或脊髓占位病变型(肉芽肿、囊肿和脓肿引起局灶性占位体征)。

脑曲霉菌感染多见于免疫功能低下的患者。中枢神经系统真菌感染途径可能是机体其他部位(如肺)真菌感染经血行播散进入颅内,或是邻近组织中的真菌感染直接向颅内蔓延。约50%的中枢神经系统真菌感染发生于健康人。此例患者未找到其他来源真菌感染的证据。常用的治疗脑曲霉菌病的药物为两性霉素B、伏立康唑、伊曲康唑、卡泊芬净[7-9]。

伏立康唑是广谱的新型抗真菌药物[10-11],对曲霉菌病的治疗效果优于其他抗真菌药[11-13],可用于治疗脑曲霉菌病,早期应用更显示其优越性[14]。伏立康唑可通过血脑屏障,且不良反应较两性霉素B和氟康唑少[6]。两性霉素B是经典的抗真菌药。应用两性霉素B大大降低了曲霉菌病的死亡率,但其大剂量的效果并不优于小剂量[15],鞘内注射少量两性霉素B可很快在脑脊液中达到有效浓度起杀菌作用。本例应用两种药物联合治疗隐球菌性脑膜炎取得了较好的疗效,有待于更多的临床研究。

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