·论著·

硝唑类脑病—2例病例报道并文献分析

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摘要 **目的:**分析硝唑类脑病的特点及预后。**方法:**收集2例硝唑类脑病患者的临床资料,并搜集相关文献进行回顾性分析。**结果:**2例患者均表现为急性亚急性起病的小脑神经系统缺损症状;MRI显示损伤部位1例为胼胝体和小脑齿状核,1例为齿状核;停药后症状均迅速好转。检索文献获得硝唑类脑病患者69例临床资料,亚裔人为41例,首发临床症状中小脑功能缺损为62例,MRI累积部位齿状核63例,患者临床症状完全恢复65例。**结论:**硝唑类脑病多累及小脑、胼胝体及脑干,尤以亚裔人多发,预后相对较好。

关键词 硝唑类脑病;齿状核;脑干;胼胝体

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Nitroimidazole Encephalopathy: Two Case Reports and Literature Analysis *KAN Shu[1], MU Ying-feng[2], WANG Wei[1], WANG Li[1], SHANG Zhen-ying[1], GENG De-qin[2]. 1. Clinical Medicine, Xuzhou Medical University, Jiangsu Xuzhou 221002, China; 2. Department of Neurology, Affiliated Hospital of Xuzhou Medical University, Jiangsu Xuzhou 221002, China*

Abstract **Objective:** To analyze the characteristics and prognosis of nitroimidazole encephalopathy. **Methods:** The clinical data of 2 patients with nitroimidazole encephalopathy were collected, and relevant literatures were collected for retrospective analysis. **Results:** The 2 patients both showed symptoms of cerebellar nervous system defect in acute or subacute onset. MRI revealed injury location to be the corpus callosum in 1 case and cerebellar dentate nucleus in the other case. Symptoms in both cases rapidly improved after stopping drug use. Literature analysis showed that, among a total of 69 patients, 41 cases were Asian, 62 cases experienced cerebellar dysfunction among first clinical symptoms, 63 cases displayed an MRI accumulation site at the dentate nucleus, and 65 cases demonstrated a complete recovery of clinical symptoms. **Conclusion:** Nitroimidazole encephalopathy involves the cerebellum, corpus callosum, and brainstem, is more prevalent in Asians, and shows relatively good prognosis.

Key words nitroimidazole encephalopathy; dentate nucleus; brain stem; corpus callosum

硝唑类药物常用于治疗厌氧菌感染,其常见的副作用有恶心、异味症、厌食和腹部不适[1],而中枢神经系统并发症较罕见。现收集2例硝唑类药物引起的中枢神经系统损害的患者资料,并结合国内外文献总结分析,以提高临床医师对本病的识别能力。

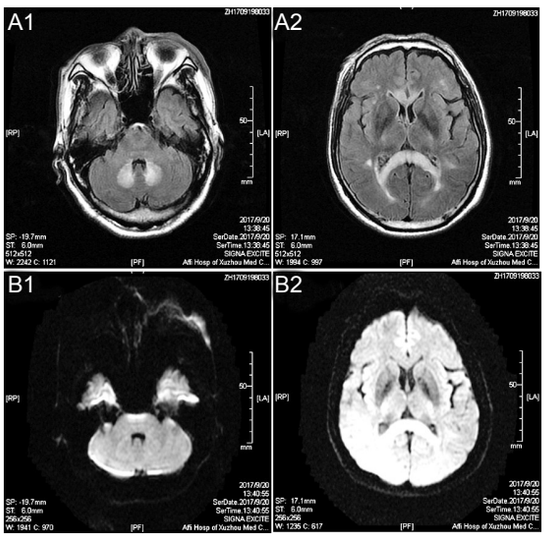
1 资料与方法

1.1 临床资料

患者男性,63岁。因"言语不清、双足麻木无力10 d"于(2017年9月16日)入院。患者10 d前无明显诱因出现双足麻木无力,呈对称性分布,伴双下肢"袜套样"感觉异常,后逐渐出现言语不清伴行走不稳。无癫痫、认知下降及精神行为异常等表现。既往史:患者眼部外伤史,就诊于南京皮肤研究所(2017年9月1日)行病变组织活检示:感染性肉芽肿可能性大,予以甲硝唑(600 mg/d)和克拉霉素口服(共服用15 d),外用夫西地酸等治疗。既往无酗酒史。婚育史、家族史未见明显异常。神经科检查:神志清楚,小脑性构音障碍,宽基步态,双下肢远端痛温觉减退。闭目难立征(+),双侧指鼻实验不准,跟-膝-胫试验(+),四肢肌力5级,双侧病理征(—)。实验室检查:白蛋白38 g/L,胆红素7.1 μmol/L,低密度脂蛋白1.59 mmol/L。血、尿、粪常规,病毒全套,同型半胱氨酸(homocysteine,Hcy),甲状腺功能,凝血功能,叶酸及维生素B_{12},男性肿瘤全套未见明显异常。影像学检查:2017年9月16日头颅CT:未见明显异常。2017年9月20日头颅MR平扫+增强示:脑内多发异常信号,以白质病变为主,增强后未见强化,见图1。2017年9月20日头颈CT血管成像(computed tomography angiography,CTA)血管未见明显狭窄或扩张。肌电图示:双下肢周围神经

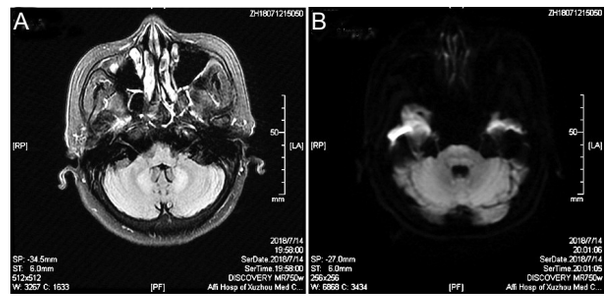
病变。定位诊断：小脑、胼胝体及周围神经。定性诊断：因患者有硝唑类药物服药史，以小脑神经缺损为主要起病形式，无发热、癫痫等症状；无酗酒史及其他毒物接触史，无相关遗传病史；血常规生化及肿瘤相关指标检查大致正常；加之典型影像学表现及肌电图表现。考虑患者为甲硝唑所致中枢神经系统及周围神经系统损害。治疗与随访：立即停用甲硝唑，加用维生素B_1，辅酶Q_{10}等。2 d后症状好转，7 d后所有症状消失出院。

患者女性，60岁。因“突发言语不清伴头晕10 d，加重1 d”就诊。患者10 d前出现言语不清伴头晕症状，入院当天晨起患者感症状加重。既往史：患者因腹泻自服奥硝唑2月，250 mg×12/d。既往无酗酒史。婚育史、家族史未见明显异常。神经科检查：神志清楚，小脑性构音障碍，宽基步态，四肢肌力5级。闭目难立征(+)，双侧指鼻实验不准，跟-膝-胫试验(+)，双侧病理征(－)。实验室检查：总胆固醇5.77 mmol/L，低密度脂蛋白3.99 mmol/L，血、尿、粪常规，病毒全套，HCY，甲状腺功能，女性肿瘤全套未见明显异常。影像学检查：2018年7月14日头颅MR提示小脑齿状核对称性异常信号，2018年7月16日头颈CTA血管未见明显狭窄或扩张，见图2。定位诊断：小脑。定性诊断：因患者有硝唑类药物服药史，起病形式为急性小脑缺损症状，无发热、癫痫等症状。无酗酒史，无其他毒物接触史，无相关遗传病史，血常规生化及肿瘤相关指标检查大致正常，加之典型的影像学表现，考虑患者为奥硝唑引起的小脑损害。治疗与随访：立即停用奥硝唑，加用维生素B_1，辅酶Q_{10}等抗氧化药物。3 d后患者症状好转，7 d后所有症状消失出院。



注：(A1-A2)T_2 FLAIR相，可见双侧小脑齿状核、胼胝体膝部及压部呈对称性高信号；(B1-B2)DWI相，可见仅胼胝体压部为高信号

图1 病例1患者头部MRI影像



注：(A)T_2 FLAIR相，可见双侧齿状核对称性高信号，呈“板栗征”；(B)DWI相，见明显异常信号

图2 病例2患者头部MRI影像

1.2 方法

收集资料并分析。通过PubMed及万方数据库，搜集2008年1月1日至2018年8月20日，以“Metronidazole、Ornidazole、Tinidazole、Nitroimidazole、encephalopathy、甲硝唑脑病、奥硝唑脑病、替硝唑脑病”及多种组合，搜索相关文献共87篇，排除非中、英文发表及综述，剩余文献59篇(英文54篇，中文5篇)。从患者种族，年龄，性别，服用药物、原因、剂量、时间，临床表现，MRI表现，是否完全恢复，恢复时MRI表现方面进行搜集整理数据。

2 结果

共69例病例，其中单独服用甲硝唑64例，替硝唑1例，奥硝唑1例；共同服用奥硝唑及甲硝唑1例，替硝唑及奥硝唑1例，替硝唑及甲硝唑1例。男性40例(58.0%)，女性29例(42.0%)；中位年龄为60岁；甲硝唑所致脑病的累计剂量的中位数为76 g。其中亚裔人为41例(59.4%)。使用硝唑类药物治疗消化道疾病为47例(68.1%)。最常出现的症状为：小脑功能缺损62例(89.9%)，精神行为异常21例(30.4%)，癫痫为5例(7.2%)。MRI累及部位齿状核63例(91.3%)、胼胝体32例(46.4%)、脑干32例(46.4%)。预后为死亡2例，残留手指刺痛感1例，轻微共济失调1例，轻度认知障碍1例，临床症状完全恢复65例(94.2 %)。39例(其中20例患者累及胼胝体压部)患者在症状好转后复查MRI，有9例(23.1%)患者影像学表现未完全恢复正常，其中8例患者为胼胝体压部异常信号。

3 讨论

甲硝唑、替硝唑、奥硝唑均属于5-硝基咪唑类化合物，通过其代谢的中间产物抑制厌氧细菌DNA的合成而杀菌[2]，被广泛用于治疗厌氧菌及原虫感染[3]。硝唑类脑病的典型临床表现为急性或亚急性起病的小脑神

经功能缺损症状、神经精神症状及癫痫，属于抗生素脑病的第3型[4]。既往有病例报道一次静脉滴注甲硝唑后出现甲硝唑脑病的案例[5]。笔者认为，即使是低剂量、短时间的接触硝唑类化合物，也可出现硝唑类脑病[6]。硝唑类脑病大部分的发病人群为亚裔，这可能与族裔及社会因素有关。本组2例从服用硝唑类药物到出现症状的时间分别为5 d和50 d，均在停药7 d左右症状消失。但好转后均未复查MRI。有报道硝唑类药物其从开始用药到出现脑病的平均时间约为3周，停药后症状恢复的中位时间为13 d[4]。第1例同时还服用大环内酯类抗生素，但其相关脑病的临床症状多为精神行为异常且MRI表现相对正常[4]，故不考虑。硝唑类脑病的病理机制尚不明确，可能与硝唑类药物干扰肠内硫胺素吸收[7]、与颅内抑制性神经递质[8,9]及RNA结合导致轴突水肿有关[10]。

对称性累及小脑齿状核、胼胝体或脑干为硝唑类脑病的常见MRI表现。典型的表现为“板栗征”[11]，为T_2 flair上由小脑齿状核对称的高信号与第三脑室共同构成（见图1、2）。其相应部位的DWI多为正常信号，表明硝唑类化合物所引起颅内水肿多为血管源性而非细胞源性。但若病变累及胼胝体压部（病例1），则T_2flair及DWI多为高信号，表明2种水肿形式共存[12,13]。文献分析表明，仅1例患者在症状恢复3 d后复查MRI，信号未恢复正常[14]，其余患者MRI未完全恢复部位均位于胼胝体压部。猜测可能在胼胝体压部存在着不同的病理生理，但具体原因尚不明确。约1/2的累及胼胝体压部的患者完全恢复，但其是否为可逆性胼胝体压部综合症的一个病因，还需研究。

鉴别诊断首先需要排除韦尼克脑病。其为硫胺素缺乏所导致的眼外肌麻痹、共济失调及精神行为异常，临床及MRI表现类似于硝唑类脑病，两者可能有相似的病理[15]。主要鉴别点为有无长期饮酒史及相关药物服用史。其他需鉴别的包括甲基溴中毒、枫糖尿病和后循环可逆性脑病综合征。甲基溴中毒也易损害小脑及脑干部位，但多合并肾功能及其他多脏器功能损伤[16]。枫糖尿病为分支链α-酮酸脱氢酶复合物的缺陷引起的先天性遗传代谢疾病，多见于新出生的婴儿[17]。而后循环可逆性脑病综合征多见于高血压患者，尤其为妊娠子痫的患者。其特征性影像学表现为包括脑后部皮质下血管源性水肿的双侧区域，在几天或几周内消退[18]。本组2例患者均无类似疾病史，故以上疾病可排除。

目前硝唑类中毒性脑病的诊断尚无统一标准，笔者提出可能的诊断标准为：①有明确硝唑类药物的接触史。②急性亚急性类似于脑血管病起病形式。③典型MRI表现为双侧小脑齿状核及胼胝体区T_2 flair上对称性高信号。④停药后症状迅速好转。⑤排除其他相关中毒代谢性疾病。本组2例均符合上述标准。

硝唑类脑病目前没有统一治疗标准，但首先最重要的是停用硝唑类化合物；其次可采取“鸡尾酒”疗法，包括使用大剂量维生素B_1[19]、左卡尼汀、辅酶Q_{10}等药物[7]；合并癫痫者可试用苯二氮卓类药物治疗[20]。

综上所述，硝唑性脑病为硝唑类化合物的罕见的神经系统并发症，亚裔人多发，多对称性的累及小脑、胼胝体、脑干等部位，出现相应的神经系统缺损症状。部分累及胼胝体压部的病变影像学上不能完全恢复。预后一般较好，多不遗留后遗症。

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LRRK2、Parkin以及PINK1均对微丝的组装和解聚具有调节作用，因此在今后的研究中明确微丝细胞是否参与PD的发病及具体的机制，并且以此为靶点开发新药物将会是一个重要的研究方向，对于PD的治疗具有指导意义。

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