

• 临床研究 •

二肽基肽酶样蛋白-6抗体相关脑炎临床特征和预后分析

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[摘要] 目的:分析二肽基肽酶样蛋白-6(dipeptidyl-peptidase-like protein 6, DPPX)抗体相关脑炎患者的临床特征。方法:对2016年1月—2025年2月南京医科大学附属脑科医院就诊的5例DPPX抗体相关脑炎患者的临床特点、脑电图、磁共振成像(magnetic resonance imaging, MRI)及预后进行回顾性研究。结果:5例均为男性,年龄14~56岁。5例患者血清DPPX抗体均为阳性,滴度1:100~1:10,其中1例合并血清接触蛋白关联蛋白2(contactin-associated protein-like 2, CASPR2)抗体阳性,4例脑脊液DPPX抗体阴性,1例滴度1:1。2例患者以行为异常起病,1例以癫痫发作起病,1例以记忆力减退起病,1例合并CASPR2抗体阳性患者以多部位游走性肌阵挛起病。4例患者头颅MRI正常,1例头颅MRI提示双侧颞叶异常信号。以癫痫发作起病的患者脑电图背景重度异常合并左前颞尖波、尖慢波频发。结论:DPPX抗体相关脑炎临床表现具有异质性,早期诊断与鉴别困难,免疫治疗有效,易复发。

[关键词] 二肽基肽酶样蛋白-6抗体相关脑炎;癫痫发作;游走性肌阵挛

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Clinical characterization and prognostic analysis of dipeptidyl-peptidase-like protein 6 antibody-associated encephalitis

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[Abstract] **Objective:** To analyze the clinical characteristics of patients diagnosed with dipeptidyl-peptidase-like protein 6(DPPX) antibody-associated encephalitis. **Methods:** A retrospective analysis was conducted on five patients with DPPX antibody-associated encephalitis admitted to the Nanjing Brain Hospital Affiliated to Nanjing Medical University between January 2016 and February 2025. Clinical characteristics, electroencephalography (EEG), magnetic resonance imaging (MRI) findings, and outcomes were reviewed. **Results:** All five patients were male, aged from 14 to 56 years. All patients tested positive for DPPX antibody in serum, with titers ranging from 1:100 to 1:10. One patient also tested positive for serum contactin-associated protein-like 2(CASPR2) antibody. Cerebrospinal fluid (CSF) DPPX antibody were negative in four patients, and positive in one patients with the titer 1:1. Two patients presented with behavioral abnormalities, one with seizures, and one with memory impairment. The patient with concurrent anti-DPPX and anti-CASPR2 antibodies presented with multifocal migratory myoclonus. Brain MRI was normal in four patients, while one patient's brain MRI indicated an abnormal signal in the bilateral temporal lobe. EEG of the patient with seizure onset showed heavy background abnormalities, accompanied by frequent sharp waves and sharp-slow waves in the left anterior temporal region. **Conclusion:** DPPX antibody-associated encephalitis is characterized by heterogeneous clinical presentations, which may complicate early diagnosis and differential diagnosis. Although immunotherapy demonstrates therapeutic efficacy, the disease remains susceptible to relapse.

[Key words] dipeptidyl peptidase-like protein 6 antibody-associated encephalitis; seizure; migratory myoclonus

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在神经元的树突和细胞体内,二肽基肽酶样蛋白-6(dipeptidyl-peptidase-like protein 6, DPPX)作为Kv4.2钾通道的调节性亚单位,发挥着关键作用,它参与了动作电位向树突的反向传播衰减过程,可有效阻止动作电位向树突扩散^[1-2]。2013年首次报道了DPPX抗体相关脑炎,其临床表现涵盖了广泛的神经系统功能障碍。具体而言,患者表现出大脑功能障碍(如记忆减退、谵妄、精神错乱、抑郁、癫痫发作)、脑干功能障碍(包括眼球运动障碍、共济失调、吞咽困难、语言障碍、呼吸衰竭)、睡眠紊乱,以及中枢神经系统过度兴奋(表现为肌阵挛、弥漫性强直、过度惊骇)。此外,还存在自主神经系统功能失调,表现为胃肠道症状(含胃排空延迟与便秘)、膀胱功能异常、心脏传导系统障碍以及体温调节障碍^[3-4]。该型脑炎可累及多系统,临床症状异质性明显。因国内有关DPPX抗体相关脑炎的研究仍相对较少,对该病认知不足,易误诊,延误治疗^[5-7]。本研究回顾了南京医科大学附属脑科医院确诊的5例DPPX抗体相关脑炎患者的临床特点,以提高对该类型脑炎的认识。

1 对象和方法

1.1 对象

纳入2016年1月—2025年2月南京医科大学附属脑科医院神经内科确诊的DPPX抗体相关脑炎患者5例。纳入标准:①急性、亚急性、隐匿性起病;②可出现一种或多种症状,包括大脑功能障碍(如记忆力减退、精神错乱)、脑干功能障碍(如眼动障碍、共济失调、吞咽困难、构音障碍、呼吸衰竭)、睡眠障碍、中枢过度兴奋(如肌阵挛、癫痫、弥漫性强直、过度惊骇、反射亢进)和自主神经功能异常(如胃肠道障碍、胃轻瘫、便秘、膀胱功能障碍、心脏传导系统障碍、体温调节障碍);③血清中DPPX抗体阳性,伴或不伴脑脊液抗体阳性。如果患者被诊断患有其他疾病,如脑瘤、病毒性脑炎、代谢性疾病和药物中毒,则被排除^[8]。本研究经南京医科大学附属脑科医院伦理委员会批准(批号:2020-KY031-01)。

1.2 方法

1.2.1 患者资料收集

收集以下患者资料:年龄、性别、神经系统症状、DPPX抗体滴度、实验室检查结果、脑电图(electroencephalography, EEG)、磁共振成像(magnetic resonance imaging, MRI)和腰椎穿刺脑脊液检查结果、治疗方案。

1.2.2 抗体检测

采用间接免疫荧光法检测细胞表面抗原,包括DPPX、N-甲基天冬氨酸受体、接触蛋白关联蛋白2(contactin-associated protein-like 2, CASPR2)的抗体。

1.2.3 随访

通过定期的门诊随访或电话随访方式收集预后信息,随访时间40~108个月。

2 结果

2.1 临床表现

回顾性分析5例DPPX抗体相关脑炎患者,临床特征详细列于表1。发病中位年龄32岁,范围14~56岁。患者3被误诊为病毒性脑炎4年。在纳入的患者中,4例表现为急性起病,1例亚急性起病。神经系统症状包括精神障碍(2例)、记忆力减退(4例)、癫痫发作(3例)、意识障碍(1例)、共济失调(1例)和睡眠障碍(1例)。患者4还出现了游走性肌阵挛,可累及一个肢体,或多个肢体同步,或从一个肢体扩散到另一个肢体。

2.2 影像学 and 实验室检测

4例患者的头颅MRI检查结果正常,其中2例EEG显示弥漫性慢波,但未观察到癫痫样放电。患者5 EEG正常,但头颅MRI提示双侧颞叶异常信号(表1)。

所有患者均接受腰椎穿刺检查。3例脑脊液蛋白升高(59.0~71.2 mg/dL)。2例白细胞升高(19~78个/mm³)。所有患者血清DPPX抗体均为阳性,滴度为1:100~1:10,其中1例脑脊液抗体滴度为1:1。患者4的血液样本中DPPX抗体和CASPR2抗体均呈阳性。2例患者的甲状腺过氧化物酶抗体和甲状腺球蛋白抗体呈阳性。所有患者副肿瘤相关抗体均为阴性。4例患者血清中弓形虫IgM、风疹病毒IgM、巨细胞病毒IgM、单纯疱疹病毒-1 IgM、单纯疱疹病毒-2 IgM均为阴性。在所有患者中均未发现肿瘤。

2.3 治疗和预后

所有患者均接受一线免疫治疗,包括甲泼尼龙(methylprednisolone, MP)和免疫球蛋白(immunoglobulin, IG)。经静脉使用IG、MP、氯硝西泮(clonazepam, CZP)、丙戊酸(valproic acid, VPA)治疗后,患者4仍出现肌阵挛,接受了另一轮静脉注射IG治疗后肌阵挛消失,随后长期服用吗替麦考酚酯(mycophenolate mofetil, MMF)、CZP、VPA。服药期间患者仍有间断性双手抖动,多次血清DPPX抗体阳性,随后又接受两次IG治疗(表1)。患者5仅接

表1 5例DPPX抗体相关脑炎患者的临床特征
Table 1 Clinical characteristics of five patients with DPPX antibody-associated encephalitis

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5
Age(years)	32	14	33	17	56
Sex	Male	Male	Male	Male	Male
Onset to diagnosis	10 days	20 days	4 years(diagnosed with viral encephalitis for 4 years)	10 days	7 months
Onset mode	Acute	Acute	Acute	Acute	Subacute
Initial symptoms	Seizure	Psychiatric disturbances	Psychiatric disturbances	Headache	Amnesia
Other symptoms	Amnesia	Amnesia, confusion	Fever, amnesia, confusion, seizure, headache, consciousness disturbance	Migrating myoclonus	Ataxia, seizure, confusion, sleep disorder
MRI	Normal	Normal	Normal	Normal	Increased signal in bilateral temporal lobe
EEG	Severe diffuse polymorphic slowing	Normal	①Normal; ②Mild diffuse polymorphic slowing; ③Mild diffuse polymorphic slowing	Normal	Normal
CSF	WBC 32/mm ³ , normal protein	Normal WBC, protein 63 mg/dL	① WBC 78/mm ³ , normal protein; ② WBC 20/mm ³ , normal protein; ③ WBC 19/mm ³ , protein 71.2 mg/dL	Normal WBC and protein	Normal WBC, protein 59 mg/dL
DPPX antibody titer	CSF(-), blood 1:100	CSF(-), blood 1:100	CSF 1:1, blood 1:10	CSF(-), blood 1:100	CSF (-), blood 1:32
Other antibody	(-)	Anti-TPO>600 U/mL, anti-TG 345.03 U/mL	Anti-TPO:126.3 U/mL, anti-TG:63.2 U/mL	Anti-CASPR2 1:10	(-)
Treatment	IG, MP, AED	IG, MP	IG, MP	IG(twice), MP, CZP, VPA	MP(twice), MMF, AED
Tumor mRS	(-)	(-)	(-)	(-)	(-)
Initial	3	3	5	2	4
Last follow-up	1	2	2	1	2
Follow-up period (months)	60	65	108	40	72

①January 6, 2016; ②March 26, 2019; ③November 29, 2019; CSF: cerebrospinal fluid; EEG: electroencephalography; WBC: white blood cell; anti-TPO: thyroid peroxidase antibody; anti-TG: thyroglobulin antibody; mRS: modified Rankin scale; IG: immunoglobulin; MP: methylprednisolone; AED: antiepileptic drugs; CZP: clonazepam; VPA: valproic acid.

受MP治疗,未接受IG治疗,复发后患者接受MP和MMF治疗。在随访期间,所有患者的改良Rankin评分均有改善。

3 结论

本研究回顾性分析了5例DPPX抗体相关脑炎

患者的临床资料,并对其临床特征进行了系统总结。所有患者均为男性,中位发病年龄为32岁。该病的发病模式呈现从急性到亚急性不等的多样性。所有患者血清DPPX抗体检测结果均为阳性,而脑脊液仅1例患者DPPX抗体呈阳性。此外,1例患者血清中同时检测到DPPX抗体和CASPR2抗体阳性。在影像学检查中,仅1例患者出现头颅MRI异常表现,EEG检查3例患者结果正常。

Kv4.2通道在神经元树突和体细胞中广泛分布。因此,DPPX抗体相关脑炎的显著临床表现涵盖了皮质、小脑、脑干、脊髓炎以及自主神经系统病变^[4,9-12]。一项多中心研究共纳入104例患者,其中58.7%出现记忆力减退,40.2%表现为精神症状,63.5%出现中枢性过度兴奋症状,包括肌阵挛、过度惊骇、癫痫发作及强直;40.4%的患者表现出脑干或小脑功能障碍,如共济失调和眼球震颤;41.3%的患者存在睡眠紊乱^[12]。本研究中,神经症状的范畴涵盖了精神障碍(2例)、记忆力减退(4例)、癫痫发作(3例)、意识障碍(1例)、共济失调(1例)以及睡眠障碍(1例)。先前的研究指出,体重减轻是该疾病的早期表现之一^[9]。研究推测,肌肠丛中DPPX的高表达可能是导致体重减轻的潜在因素^[3]。自主神经系统功能障碍症状涵盖腹泻、胃轻瘫、便秘、尿路功能障碍、体温波动性降低或升高、无症状性室性心动过速以及心脏骤停^[4]。本研究未发现体重减轻及自主神经系统功能障碍症状。胃肠道问题与自主神经系统功能障碍症状的出现可能与种族因素相关^[11]。

中枢性过度兴奋的临床表现包括过度惊骇、肌阵挛、弥漫性强直以及反射亢进,这些症状在DPPX的抗体相关脑炎患者中尤为普遍^[4,9,12]。过度惊骇和僵硬/强直可被认为是伴有强直和肌阵挛的进行性脑脊髓炎(progressive encephalomyelitis, rigidity, and myoclonus, PERM)的主要表现^[13-16]。与PERM相关的抗体包括甘氨酸受体抗体、amphiphysin蛋白抗体以及GAD65抗体^[16-17]。先前的文献报道了5例DPPX抗体相关脑炎患者进展为PERM^[9,18]。本研究未观察到类似病例。然而,在血清DPPX抗体和CASPR2抗体均呈阳性的患者4中,观察到了游走性肌阵挛的现象。这些发作具有以下特征:①发作突然且短暂;②表现形式多样,可能仅涉及单一肢体,或同时影响多个肢体,甚至可能从一个肢体蔓延至另一个肢体。在这些发作过程中,并未检测到癫痫放电现象。先前的研究表明,40%(8/20)的DPPX抗体相关脑炎患者会出现肌阵挛症状^[4]。CASPR2属

于轴突蛋白家族中的细胞黏附分子,在中枢神经系统及周围神经系统轴突中均有表达,是神经元电压门控钾通道复合体自身抗体的主要靶抗原^[19-20]。肌阵挛现象也可在CASPR2抗体相关脑炎患者中观察到^[19-20]。例如,在CASPR2抗体相关脑炎患者中,站立或行走时下肢肌阵挛收缩、节段性脊髓肌阵挛导致躯干屈曲以及上肢和下肢肌张力障碍伴叠加肌阵挛(左侧为主)的现象均有报道^[21-24]。然而,DPPX抗体相关脑炎和CASPR2抗体相关脑炎患者中未见游走性肌阵挛现象^[4,19-24]。在患者4中,DPPX抗体与CASPR2抗体的共同作用可能诱发了游走性肌阵挛。该患者接受了IG、MP、CZP和VPA的治疗方案。治疗1个月后,仍有肌阵挛现象,患者接受第2次IG治疗,并随后出院。出院后,患者长期服用MMF、CZP及VPA,随访期间出现双手震颤症状。多次检测显示血清中DPPX抗体呈阳性,随后患者又接受了两次IG治疗。

本研究中1例患者出现了复发。然而,因为临床随访时间不足,复发率很可能被低估。DPPX抗体相关脑炎患者的总体死亡率为5.8%,这些死亡主要是由并发症所致^[12]。

DPPX抗体相关脑炎十分罕见,目前尚无基于循证医学的治疗指南或公认的治疗共识。免疫抑制治疗仍是主要的治疗方法,早期治疗预后较好。对于一些合并肿瘤的患者,肿瘤治疗也至关重要。提高对此类型脑炎的认识,有助于早期诊断,早期治疗。

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Author's Contributions:

HU Xiuxiu was responsible for data collection, analysis, and manuscript writing. MIAO Ailiang was responsible for clinical follow-up, research guidance, and paper review.

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