·神经病理学专家论坛·

β-淀粉样蛋白相关性中枢神经系统血管炎

李卓 朴月善 卢德宏

【摘要】 淀粉样脑血管病相关性中枢神经系统血管炎亦称为β-淀粉样蛋白(Aβ)相关性中枢神经系统血管炎,主要表现为存在Aβ沉积的小血管壁或其周围慢性炎症性改变。考虑部分患者临床表现、脑脊液和影像学表现不典型,明确诊断仍需依靠脑组织活检。本文拟就其发病机制、病理学特征、临床表现、治疗及预后等进展进行概述。

【关键词】 淀粉样β蛋白; 血管炎,中枢神经系统; 病理学; 综述

Amyloid β-related central nervous system vasculitis

LI Zhuo, PIAO Yue-shan, LU De-hong
Department of Pathology, Xuanwu Hospital, Capital Medical University, Beijing 100053, China
Corresponding author: LU De-hong (Email: ludehong05@sina.com.cn)

【**Abstract**】 Amyloid β (Aβ)-related central nervous system (CNS) vasculitis, which is also known as cerebral amyloid angiopathy (CAA)-related CNS vasculitis, is characterized by the presence of chronic inflammation within or around the walls of Aβ-deposit blood vessels. Cerebral biopsy is the gold standard for diagnosis of Aβ-related CNS vasculitis considering the atypical clinical features, cerebrospinal fluid (CSF) and neuroimaging findings of some patients. This paper reviewed the pathogenesis, neuropathology, clinical features, treatment and prognosis of Aβ-related CNS vasculitis.

【**Key words**】 Amyloid beta-protein; Vasculitis, central nervous system; Pathology; Review

淀粉样脑血管病(CAA)是以淀粉样蛋白沉积于大脑皮质和软脑膜血管壁为主要病理学特征的中枢神经系统小血管病变,主要发生于颅内小动脉,较少发生于静脉和毛细血管。根据所沉积的淀粉样蛋白种类[包括β-淀粉样蛋白(Aβ)、淀粉样胱抑素C(ACys-C)、淀粉样朊蛋白(APrP)、ABri/ADan蛋白(ABri/ADan)、淀粉样运甲状腺素蛋白(ATTR)、淀粉样凝溶胶蛋白(AGel)和淀粉样免疫球蛋白轻链]分为7种类型(表1),其中,Aβ沉积导致的淀粉样脑血管病在老年患者,特别是阿尔茨海默病(AD)患者中最为常见[1]。淀粉样脑血管病主要表现为单发或多发脑叶出血,也可以出现反复发生的不同脑叶出血[2-3]。血管壁沉积的Aβ可引起单核吞噬细胞相关性免疫应答反应,病变血管常伴有明显炎症性改变,故称为Aβ相关性中枢神经系统血管炎(以下简称Aβ相关性血管炎)[1,4],以急性或亚急性认知功能障碍、癫痫发作和头痛为主要临床表现。

1974年,Reid和Maloney[5]首次报告经脑组织活检证实的多核巨细胞浸润性淀粉样脑血管病,但并未对其进行详细的临床病理学阐述。1987年,卢德宏[3]首次对淀粉样脑血管病及其主要并发症特点和神经病理学改变进行描述,逐渐引起国内学者对该病的重视。2004年,Eng等[6]报告42例淀粉样脑血管病患者,其中7例(16.67%)经脑组织活检证实大脑皮质或软脑膜发生Aβ沉积的血管周围存在单核细胞和多核巨细胞聚集,该项研究还对此7例存在血管周围炎性浸润患者与其余35例无炎症反应患者的临床表现、实验室和影像学检查、治疗及预后等资料进行比较,阐明了Aβ相关性血管炎的临床特点,自此引起对该病的重视。2010年,Chung等[7]对72例Aβ相关性血管炎患者的临床资料进行总结分析,并首次提出该病诊断标准;考虑到部分患者临床症状和影像学改变不典型,仍需依靠脑组织活检作出明确诊断[8]。

一、发病机制

病变血管内沉积的Aβ由神经元及其他脑实质

doi:10.3969/j.issn.1672-6731.2016.01.002
作者单位:100053 北京,首都医科大学宣武医院病理科
通讯作者:卢德宏(Email:ludehong05@sina.com.cn)

表1 淀粉样脑血管病分类[11]

Table 1. Classification of CAA[11]

Amyloid protein	Clinical phenotype
Aβ	Sporadic CAA Associated with: aging, sporadic AD, other conditions, including vascular malformations Hereditary or genetic: Down´s syndrome HCHWA-D
ACys-C	HCHWA-I
APrP	Prion disease
ABri/ADan	FBD/FDD
ATTR	Meningocerebrovascular involvement of familial transthyretin amyloidosis
AGel	Meningocerebrovascular involvement of gelsolin-related amyloidosis
Immunoglobulin light chain amyloid	CAA with leukoencephalopathy due to brain-restricted monoclonal plasma cell proliferation

Aβ, amyloid β-protein, β-淀粉样蛋白; ACys-C, amyloid cystatin C, 淀粉样胱抑素C; APrP, amyloid Prion protein, 淀粉样朊蛋白; ATTR, amyloid transthyretin, 淀粉样运甲状腺素蛋白; AGel, amyloid gelsolin, 淀粉样凝溶胶蛋白; CAA, cerebral amyloid angiopathy, 淀粉样脑血管病; AD, Alzheimer´s disease, 阿尔茨海默病; HCHWA-D, hereditary cerebral hemorrhage with amyloidosis-Dutch type, 荷兰淀粉样变性相关性遗传性脑出血; HCHWA-I, hereditary cerebral hemorrhage with amyloidosis-Icelandic type, 冰岛淀粉样变性相关性遗传性脑出血; FBD, familial British dementia, 英国家族性痴呆; FDD, familial Danish dementia, 丹麦家族性痴呆

细胞产生,并经血-脑屏障转运作用、血管周围间隙排泄作用、细胞吞噬作用和酶降解作用等方式消除,Aβ产生和消除机制失衡可以导致Aβ沉积。Aβ沉积于血管壁引起的血管病变是脑叶出血、认知功能障碍和痴呆的重要原因之一。研究显示,Aβ相关性血管炎患者的血管炎症性改变仅发生于存在Aβ沉积的血管,免疫组织化学染色和特殊染色提示部分Aβ可被表达主要组织相容性复合物Ⅱ(MHC Ⅱ)的吞噬细胞吞噬[9]。考虑其病理学特点,有学者认为,Aβ沉积于血管壁引起的自主免疫反应是导致血管炎的主要原因,但也不能排除血管炎促进Aβ沉积的可能,而Aβ相关性血管炎仅表现为肉芽肿性血管炎的机制尚不十分清楚[10-11]。

二、病理学特征

Aβ相关性血管炎为大脑皮质和软脑膜发生Aβ沉积的小血管壁或其周围慢性炎症性改变,伴或不伴软脑膜增厚。大体标本观察可见,软脑膜增厚、广泛性脑萎缩、大脑皮质多发梗死灶[12],也可表现为大脑皮质新发或陈旧性出血伴蛛网膜下隙出血和广泛性血管源性脑水肿致中线结构偏移[13]。光学显微镜观察,淀粉样脑血管病背景下血管壁或其周围淋巴细胞浸润、多核巨细胞和巨噬细胞构成的肉芽肿形成(图1a),常伴血管壁正常结构解离、纤维素样坏死、血管腔血栓形成和再通,病变血管周围含有含铁血黄素的吞噬细胞聚集,血管周围脑梗死改变,主要发生于大脑皮质浅层(图1b);部分患者可见脑白质神经胶质细胞增生或疏松,脑白质内小血管发生轻度退行性变,但未见Aβ沉积和血管周围炎症性改变;刚果红染色病变血管呈砖红色,偏振光显微镜观察刚果红染色阳性部位呈苹果绿色双折光(图2)。免疫组织化学染色,病变血管壁内沉积的Aβ主要为$Aβ_{1\sim40}$,部分为$Aβ_{1\sim42}$,存在$Aβ_{1\sim42}$沉积者常伴阿尔茨海默病表现(图3a,3b)。少数病例脑组织活检可见部分病变血管呈急性炎症性改变,但未见明确的多核巨细胞浸润,免疫组织化学染色呈阴性,因此有学者认为这可能是由于急性炎症反应清除血管壁内沉积的Aβ所致。免疫组织化学染色病变血管周围巨噬细胞CD68呈阳性(图3c),巨噬细胞内可见被吞噬的Aβ,血管周围亦可见$CD3^+$T细胞和$CD20^+$B细胞浸润[9,12,14]。Aβ相关性血管炎发生于大脑皮质或软脑膜小血管,脑白质内血管多不受累。鉴于大多数Aβ相关性血管炎患者T_2WI和FLAIR成像表现为白质内斑片状或融合性不对称高信号[7],因此有学者认为可能与软脑膜血管Aβ沉积导致脑深部白质低灌注、神经细胞缺血变性有关[15]。

三、临床特点

Aβ相关性血管炎平均发病年龄约65岁,主要表现为认知功能障碍或行为改变,轻者可仅以轻度认知损害(MCI)为主,重者可出现昏迷。结合其神经病理学改变,考虑是由于脑深部白质低灌注导致的皮质-皮质下环路损害[16]。约半数患者可以出现局限性神经功能缺损,如轻偏瘫、偏身感觉障碍、失语、偏盲和小脑共济失调;少数表现为癫痫发作、头痛或短暂性脑缺血发作(TIA)。大多数患者表现为2~4种临床症状并存[9,17]。腰椎穿刺脑脊液检查多可见蛋白定量升高,仅少数患者呈现淋巴细胞比例轻度增加、红细胞沉降率(ESR)升高,经免疫抑制剂治疗后均可恢复正常[18]。典型的头部MRI表现为钆增强后软脑膜局灶性强化[4],T_2WI和FLAIR成像呈非对称性双侧脑白质高信号,增强后脑实质表现为点灶样强化(图4),部分患者磁敏感加权成像(SWI)呈现额顶枕叶脑沟周围皮质微出血[9]。

四、治疗与预后

治疗原则包括糖皮质激素冲击和免疫抑制剂

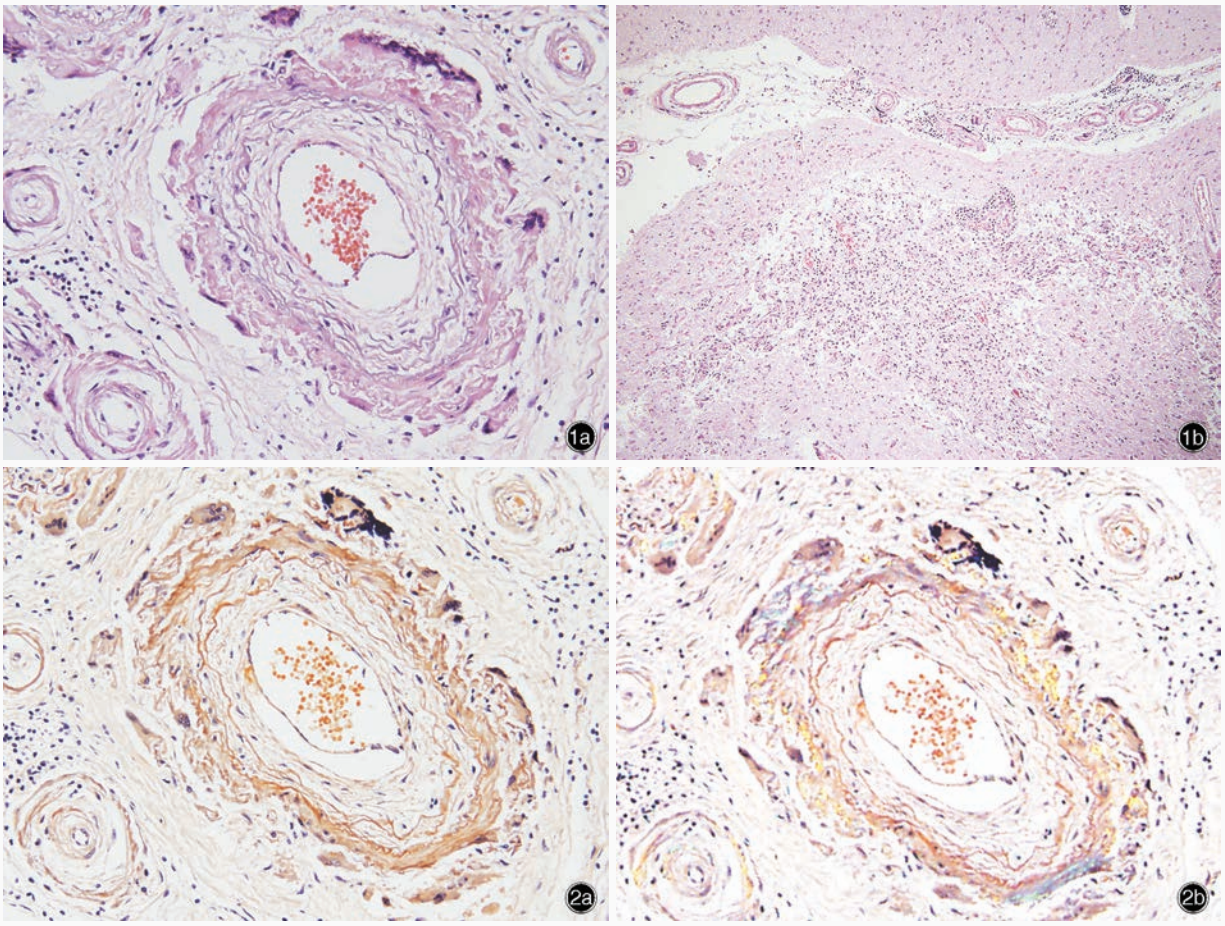

图1 光学显微镜观察所见 HE染色 1a 血管壁淀粉样变性，血管壁及其周围炎症性改变，淋巴细胞和多核巨细胞浸润 ×200 1b 软脑膜部分血管壁淀粉样变性，血管壁及其周围可见淋巴细胞和多核巨细胞浸润，病变血管周围皮质浅层正常结构消失、神经元缺失、神经胶质细胞增生，大量吞噬细胞呈灶状浸润，呈脑梗死改变 ×100 **图2** 光学显微镜观察所见 刚果红染色 ×200 2a 小动脉壁呈砖红色 2b 偏振光显微镜观察，刚果红染色阳性部位呈苹果绿色双折光，提示Aβ沉积

Figure 1 Optical microscopy findings HE staining Amyloid deposition, perivascular inflammation, infiltration of lymphocytes and multinuclear giant cells were observed. ×200 (Panel 1a) Amyloid deposition, infiltration of lymphocytes and multinuclear giant cells could be observed within and surround the wall of leptomeningeal arteriole. Superficial cortex around the blood vessel with vasculitis lost its normal structure and showed infarction, which was characterized by loss of neurons, gliocyte proliferation, and focal infiltration of a large number of phagocytes. ×100 (Panel 1b) **Figure 2** Optical microscopy findings Congo red staining ×200 The wall of arteriole was brick-red (Panel 2a). Polarized light showed apple green birefringence, confirming that the red staining was due to Aβ deposition (Panel 2b).

治疗，应根据患者临床表现、病情演变、预后评价及伴随疾病进行个体化治疗。大多数患者对糖皮质激素和免疫抑制剂有效，可恢复至发病前状态，部分患者可能在减药或停药后复发，免疫抑制剂治疗仍然有效，但也有极少数患者因过度治疗病残或病死[4,9]。个别患者需同时应用苯妥英钠以预防癫痫发作，但停药后再次出现癫痫发作[18]。

五、与其他相关疾病的关系

Aβ相关性血管炎、原发性中枢神经系统血管炎和淀粉样脑血管病在临床表现、影像学特点、治疗及预后等方面存在众多异同之处。(1)原发性中枢神经系统血管炎：可发生于任何年龄段，但以40～60岁人群好发，临床表现为脑实质、脊髓和软脑膜供血的中小动脉和静脉炎症性改变，可引起脑组织缺血、脑叶或局部皮质或皮质下点灶状出血，极少数可出现蛛网膜下隙出血，偶可累及大血管[19]。患者多以头痛为首发症状，可伴感觉异常、认知功能障碍等。腰椎穿刺脑脊液检查蛋白定量和淋巴细胞计数升高，葡萄糖正常[20]；T_2WI显示幕上不对称性多发高信号[19]。Salvarani等[17]对梅奥诊所1987–2011年诊断与治疗的28例Aβ相关性血管炎和1983–2007年收治的118例原发性中枢神经系统

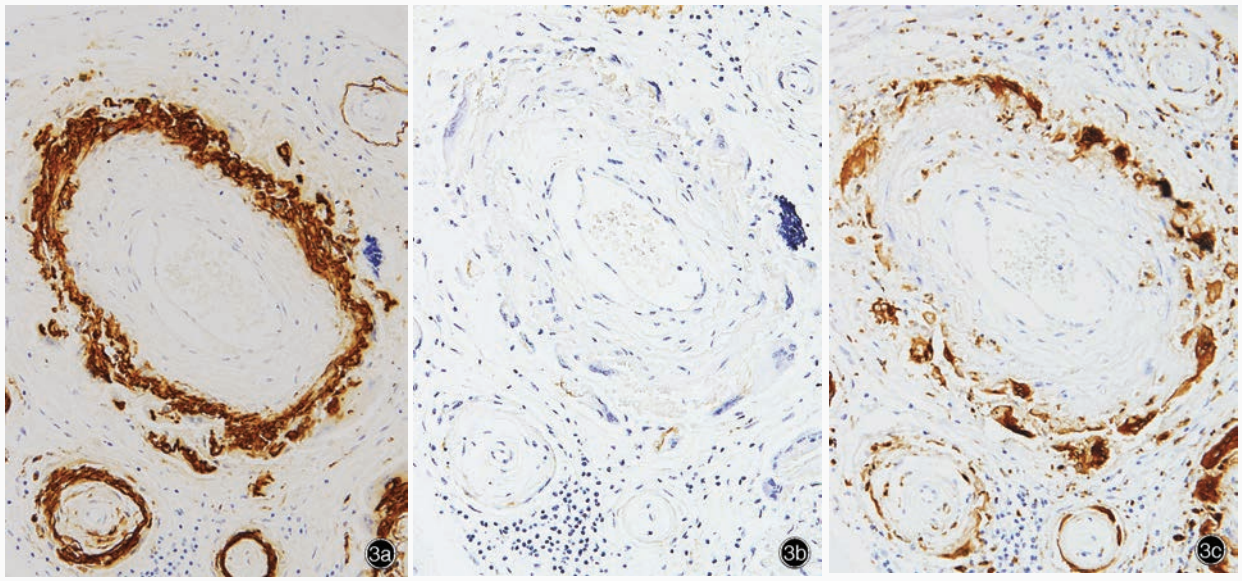

图3　光学显微镜观察所见　免疫组织化学染色(EnVision二步法)　×200　3a　血管壁$A\beta_{1-40}$呈阳性　3b　血管壁$A\beta_{1-42}$呈阴性　3c　血管壁浸润的多核巨细胞CD68呈阳性

Figure 3　Optical microscopy findings　Immunohistochemical staining (EnVision)　×200　The wall of arteries was positive for $A\beta_{1-40}$ (Panel 3a). The wall of arteries was negative for $A\beta_{1-42}$ (Panel 3b). Multinuclear giant cells infiltrated into the wall of arteries and were positive for CD68 (Panel 3c).

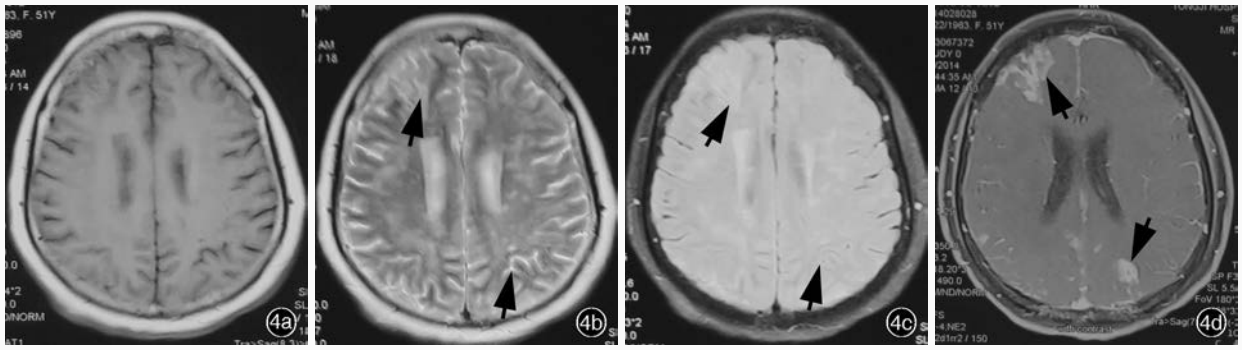

图4　女性患者,51岁,主因头痛1个月、意识障碍4 d入院。临床诊断为意识障碍待查。入院后头部MRI检查所见　4a　横断面T_1WI显示右侧额叶脑沟变浅,异常信号不明显　4b　横断面T_2WI显示,双侧大脑半球皮质和皮质下白质多发斑片状稍高信号(箭头所示)　4c　横断面FLAIR成像显示右侧皮质肿胀呈高信号;双侧额顶叶皮质下多发斑片状高信号(箭头所示)　4d　横断面增强T_1WI显示右侧额叶皮质和皮质下、双侧顶叶皮质下多发斑片状强化(箭头所示)

Figure 4　A 51-year-old female presented headache for one month and conscious disturbance for 4 d, and was diagnosed as conscious disturbance yet to be investigated. Cranial MRI findings after admission　Axial T_1WI showed the sulci in right frontal lobe became shallow, with unobvious abnormal signal (Panel 4a). Axial T_2WI demonstrated multiple patchy slight high-intensity signals in cortical and subcortical white matter of bilateral cerebral hemispheres (arrows indicate, Panel 4b). Axial FLAIR demonstrated high-intensity signal of right cortex and multiple patchy high-intensity signals of bilateral fronto-parietal cortex (arrows indicate, Panel 4c). Axial contrast-enhanced T_1WI demonstrated mulifocal patchy enhancement of right frontal cortex and subcortex, and bilateral parietal subcortex (arrows indicate, Panel 4d).

血管炎患者的临床和病理学特征进行回顾分析,其结论为:Aβ相关性血管炎较原发性中枢神经系统血管炎发病年龄更晚,更易出现认知功能障碍和意识障碍,且轻偏瘫、视力障碍或脑梗死发生率更低。也有研究发现,Aβ相关性血管炎患者脑脊液蛋白定量高于原发性中枢神经系统血管炎,且免疫抑制剂对前者的疗效优于后者[4];原发性中枢神经系统血管炎需抗凝治疗,而Aβ相关性血管炎则应避免抗凝治疗以减少脑出血风险[21]。(2)淀粉样脑血管病:发病率随年龄的增长而逐渐增加。Aβ相关性血管炎的发病年龄更早,认知功能障碍、神经功能缺损、脑卒中或脑出血症状更少见,钆增强软脑膜强化更明显,对药物治疗敏感性和预后更佳,均提示血管炎症反应可能是引起临床症状的主要因素[17]。通过对Aβ相关性血管炎、原发性中枢神经系统血管炎和淀粉样脑血管病的比较,发现前两者存在更多相似

之处，提示Aβ相关性血管炎应考虑为仅表现为肉芽肿性血管炎的原发性中枢神经系统血管炎的一种亚型[11,17]。

参 考 文 献

[1] Yamada M. Cerebral amyloid angiopathy: emerging concepts. J Stroke, 2015, 17:17-30.

[2] Vinters HV. Cerebral amyloid angiopathy: a critical review. Stroke, 1987, 18:311-324.

[3] Lu DH. Neuropathology of cerebral amyloid angiopathy. Zhongguo Shen Jing Jing Shen Ji Bing Za Zhi, 1987, 13:184-186.[卢德宏. 大脑类淀粉血管病的神经病理学. 中国神经精神疾病杂志, 1987, 13:184-186.]

[4] Nouh A, Borys E, Gierut AK, Jose B, Biller J. Amyloid-beta related angiitis of the central nervous system: case report and topic review. Front Neurol, 2014, 5:13.

[5] Reid AH, Maloney AF. Giant cell arteritis and arteriolitis associated with amyloid angiopathy in an elderly mongol. Acta Neuropathol, 1974, 27:131-137.

[6] Eng JA, Frosch MP, Choi K, Rebect W, Greenberg SM. Clinical manifestations of cerebral amyloid angiopathy - related inflammation. Ann Neurol, 2004, 55:250-256.

[7] Chung KK, Anderson NE, Hutchinson D, Synek B, Baeber PA. Cerebral amyloid angiopathy related inflammation: three case reports and a review. J Neurol Neurosurg Psychiatry, 2010, 82: 20-26.

[8] Lu DH, Piao YS, Ruan QY. Devote much attention to neuropathology study of meningeal diffuse lesions. Zhongguo Xian Dai Shen Jing Ji Bing Za Zhi, 2011, 11:491-494.[卢德宏, 朴月善, 阮清源. 应重视脑膜弥漫性病变的神经病理学研究. 中国现代神经疾病杂志, 2011, 11:491-494.]

[9] Danve A, Grafe M, Deodhar A. Amyloid beta-related angiitis: a case report and comprehensive review of literature of 94 cases. Semin Arthritis Rheum, 2014, 44:86-92.

[10] Bogner S, Bernreuther C, Matschke J, Barrera-Ocampo A, Sepulveda-Falla D, Leypoldt F, Magnus T, Haag F, Bergmann M, Brück W, Vogelgesang S, Glatzel M. Immune activation in amyloid - β - related angiitis correlates with decreased parenchymal amyloid-β plaque load. Neurodegener Dis, 2014, 13:38-44.

[11] Fang CW, Chen YC, Liao IC, Lin CC. Primary granulomatous angiitis of the central nervous system with amyloid angiopathy. Neurologist, 2015, 19:73-78.

[12] Sakai K, Hayashi S, Sanpei K, Yamada M, Takahashi H. Multiple cerebral infarcts with a few vasculitic lesions in the chronic stage of cerebral amyloid angiopathy - related inflammation. Neuropathology, 2012, 32:551-556.

[13] Szpak GM, Lewandowska E, Sliwińska A, Stępień T, Tarka S, Mendel T, Rafałowska J. Inflammatory cerebral amyloid angiopathy: the overlap of perivascular (PAN - like) with vasculitic (Aβ-related angiitis) form. An autopsy case. Folia Neuropathol, 2011, 49:335-347.

[14] Scolding NJ, Joseph F, Kirby PA, Mazanti I, Gray F, Mikol J, Ellison D, Hilton DA, Williams TL, MacKenzie JM, Xuereb JH, Love S. Abeta-related angiitis: primary angiitis of the central nervous system associated with cerebral amyloid angiopathy. Brain, 2005, 128:500-515.

[15] Oide T, Tokuda T, Takei Y, Takahashi H, Ito K, Ikeda S. Serial CT and MRI findings in a patient with isolated angiitis of the central nervous system associated with cerebral amyloid angiopathy. Amyloid, 2002, 9:256-262.

[16] Roman GC, Erkinjuntti T, Wallin A, Pantoni L, Chui HC. Subcortical ischaemic vascular dementia. Lancet Neurol, 2002, 1:426-436.

[17] Salvarani C, Hunder GG, Morris JM, Brown RD, Christianson T, Giannini C. Aβ-related angiitis: comparison with CAA without inflammation and primary CNS vasculitis. Neurology, 2013, 81:1596-1603.

[18] Schwab P, Lidov HG, Schwartz RB, Anderson RJ. Cerebral amyloid angiopathy associated with primary angiitis of the central nervous system: report of 2 cases and review of the literature. Arthritis Rheum, 2003, 49:421-427.

[19] Pourmahmoodian H, Ghelichnia Omrani HA, Harrirchian MH, Ghabaee M, Zamani B, Ghaffarpour M. Primary angiitis of the central nervous system. Acta Med Iran, 2012, 50:216-221.

[20] Vera-Lastra O, Sepúlveda-Delgado J, Cruz-Domínguez Mdel P, Medina G, Casarrubias-Ramírez M, Molina-Carrión LE, Pineda-Galindo LF, Olvera-Acevedo A, Hernández-Gonzalez C, Jara LJ. Primary and secondary central nervous system vasculitis: clinical manifestations, laboratory findings, neuroimaging, and treatment analysis. Clin Rheumatol, 2015, 34:729-738.

[21] Ishii M, Lavi E, Kamel H, Gupta A, Ladecola C, Navi BB. Amyloid β-related central nervous system angiitis presenting with an isolated seizure. Neurohospitalist, 2014, 4:86-89.

（收稿日期：2015-12-30）

·小词典·

中英文对照名词词汇(一)

阿尔茨海默病 Alzheimer's disease(AD)

比值比 odds ratio(OR)

标准化均数差 standardized mean difference(SMD)

迟发性阿尔茨海默病 late onset Alzheimer's disease(LOAD)

重组组织型纤溶酶原激活物 recombinant tissue-type plasminogen activator(rt-PA)

促甲状腺激素 thyroid stimulating hormone(TSH)

大脑后动脉 posterior cerebral artery(PCA)

大脑中动脉 middle cerebral artery(MCA)

大脑中动脉闭塞 middle cerebral artery occlusion(MCAO)

大脑中动脉高密度征 hyperdense middle cerebral artery sign(HMCAS)

单一部位脑出血 solitary intracerebral hemorrhage(SICH)

电压门控性钠离子通道 voltage-gated sodium channel(VGSC)

β-淀粉样蛋白 amyloid β-protein(Aβ)

淀粉样脑血管病 cerebral amyloid angiopathy(CAA)

动-静脉畸形 arteriovenous malformation(AVM)

短暂性脑缺血发作 transient ischemic attack(TIA)