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脑小血管病的病因和发病机制的最新进展

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摘　要： 脑小血管病(CSVD)是一种大脑微血管疾病,是脑卒中的常见原因,也是导致老年人认知障碍的主要原因,但其发病机制尚不清楚,本文对目前主要的脑小血管病的病因及发病机制进行综述,为临床对该病的诊治提供参考。

关键词： 脑小血管病；　发病机制
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Latest advances in the etiology and pathogenesis of small cerebral vessel disease　*ZHANG Yang, HE Li.* (*Department Neurology, West China Hospital, Sichuan University, Chengdu* 610041, *China*)

Abstract: Cerebral small vessel disease (CSVD) is a cerebral microvascular disease and is a common cause of stroke and a major cause of cognitive impairment in the elderly, but its pathogenesis remains unclear. This article reviews the main etiologies and pathogeneses of CSVD, in order to provide a reference for the clinical diagnosis and treatment of the disease.

Key words: Cerebral small vessel disease;　Pathogenesis

脑小血管病(cerebral small vessel disease,CSVD),是指主要涉及大脑小血管(直径40~200 μm)、毛细血管和小静脉病变导致一系列临床、影像和病理改变的综合征。目前对于脑小血管的定义更为宽泛,不仅包括上述小血管,还包括这些小血管周围2~5 mm的脑实质和蛛网膜下腔内的血管结构[1]。

1　脑小血管病的病因

多数CSVD是散发性的,主要的危险因素为高血压,研究显示,无论是舒张压还是收缩压,都与CSVD发病显著相关[2, 3]。高血压也与正常人脑白质微结构的损伤有关[4]。但是年龄、糖尿病、高脂血症、饮酒、吸烟及过量的食盐摄入也是主要的危险因素[5]。除了散发性的CSVD之外,也包括遗传性(基因相关性)小血管病变,炎症及免疫介导的小血管病,静脉胶原病及其他小血管病变等[6]。

CSVD根据病因分为以下分型:I型,小动脉硬化;II型,散发性或遗传性脑淀粉样血管病(cerebral amyloid angiopathy,CAA);III型,其他遗传性CSVD;IV型,炎症或免疫介导的小血管病;V型,静脉胶原病;VI型,其他小血管病[7]。

2　脑小血管病的发病机制

近年来研究认为,CSVD可能是一种全脑动态疾病,各种致病因素在发病过程中都有相互作用[8]。

2.1　动脉粥样硬化　动脉粥样硬化是CSVD最常见的发病机制。高血压、高龄、血糖控制较差、吸烟、高同型半胱氨酸浓度、肥胖和血脂异常被认为是导致小动脉硬化的原因。病理生理机制主要是由于年龄的增加,加上高血压和糖尿病等因素的促进作用,小动脉中膜出现平滑肌细胞丢失,血管壁上缺乏脂质沉积,内弹力膜退化,成纤维细胞增殖,出现玻璃样变,纤维素样坏死,使血管管壁狭窄。免疫组化研究显示,小血管壁层纤维化是由于纤维胶原I型和III型沉积所致[9]。此外,管壁损伤导致其外部因纤维化而膨胀,成为微动脉瘤,近端管腔狭窄或梗阻[10]。

2.2　脑淀粉样血管病(CAA)　CAA与高血压或其他传统的血管风险因素无关。CAA通常与年龄、注意力缺失和*APOEe4*等位基因有关。CAA通常与AD相关的淀粉样斑块同时出现,主要局限于皮质灰质,皮质下白质不受影响[11]。目前对于CAA造成认知障碍和卒中的机制还不明确[12],有研究认为β淀粉样蛋白沉积可能参与到血管堵塞和血管破裂的病理过程中[13]。

2.3　血脑屏障(blood-brain barrier, BBB)障碍　局部BBB的功能障碍也有可能导致CSVD的血管病变以及相关脑实质病变[14]。在病理情况下,BBB的渗透性变化导致血浆或者细胞成分从血管中渗漏,造成脑微血管损伤、脑组织水肿和炎症[15, 16]。并且大量研究表明,BBB渗透性变化导致渗漏是CSVD常见的特点,由此可见,BBB受损引起功能障碍是CSVD关键的发病机制[17, 18]。

2.4　慢性低灌注　脑血流受损是内皮功能障碍的另一表现,但脑血流与小血管病变形成的关系目前尚不清楚。小动脉纤维化与弥漫性白质损伤可能是由慢性低灌注联系起来的。小动脉扩张不足导致脑组织反复灌注不足,可引起脑组织的累积性损

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害，引起髓鞘结构被破坏、部分轴突丢失、BBB功能障碍、小胶质细胞和巨噬细胞聚集以及星形胶质细胞活性增强，这些特征与腔隙性脑梗死性质相似。大脑慢性低灌注、水肿和BBB功能障碍在CSVD的发病过程中都是相互依存的[19, 20]。

2.5 遗传因素 伴皮质下梗死和白质脑病的常染色体显性遗传性脑动脉病（cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy，CADASIL）是最常见的单基因脑小血管，该病变的基因定位在19p13.2-13.1的*NOTCH3*基因。目前研究已经报道近200种*NOTCH3*基因不同的突变方式。其次常见的是CADASIL2，是由常染色体显性基因*HTRA*突变造成的。同时，*HTRA1*基因也是导致伴皮质下梗死和白质脑病的常染色体隐性遗传性脑动脉病（cerebral recessive dominant arteriopathy with subcortical infarcts and leukoencephalopathy，CARASIL）的致病基因。CADASIL和CADASIL2的临床表现主要包括伴有先兆的偏头痛、早发性腔隙性脑梗死、脑病、抑郁和早发性痴呆[21, 22]。

*COL4A1*和*COL4A2*基因突变导致IV型胶原蛋白α链合成障碍，导致血管壁结构改变，脆性增加。患者出现脑小血管病变，肾病等。

近年来对单基因CSVD患者尸检和单基因疾病动物模型的蛋白质组学和生化研究表明，不同类型的单基因疾病之间的疾病通路可能是共享的，*NOTCH3*和*HTRA1*基因突变可能通过相似的途径涉及细胞外基质ECM功能的损伤，导致CSVD[22, 23]。

3 总 结

脑小血管病为近年来临床研究的热点，全面了解其发病机制及病理生理变化能帮助我们对该病的认识不断深入，为早期识别及干预提供重要的研究方向。

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