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·综述·

脑外伤与脑血管病所致认知障碍发生机制的研究进展

孙新亭[1] 张小年[1] 张 皓[1,2]

认知是指个体认识和理解事物的心理过程,包括对自己与环境的确定、感知、注意、学习和记忆、思维和语言等。认知功能由多个认知域组成,包括记忆、计算、时空间定向、结构能力、执行能力、语言理解和表达及应用等方面。认知功能障碍泛指各种原因导致的不同程度的认知功能损害(cognitive impairments),从轻度认知功能损害到痴呆。认知功能障碍又称为认知功能衰退、认知功能缺损或认知残疾。

近年来随着神经及精神科学的发展,认知功能障碍逐渐成为研究热点。脑血管病(cerebral vascular disease)和脑外伤(traumatic brain injury)是除了阿尔茨海默病(Alzheimer disease)之外导致认知障碍的两类常见的神经系统疾病,均可通过损害脑部神经组织,引起脑内结构和功能的变化,最终损害认知功能,两者机制虽有相似,但并不完全相同。探索两者发病机制上的异同点,对于这两类疾病所致认知障碍的诊断、治疗、康复及预后判断都很重要。

1 认知障碍的发生机制

引起认知功能障碍的机制十分复杂,目前尚不完全清楚。根据现有的资料,认知障碍的形成机制大致分为两个方面:即认知相关脑组织结构的破坏以及神经递质系统的异

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1 首都医科大学康复医学院,中国康复研究中心北京博爱医院,北京,100068; 2 通讯作者
作者简介:孙新亭,男,博士,主治医师; 收稿日期:2013-02-21

常。大脑的很多部位都参与认知功能的正常表达,例如额叶、颞叶、顶叶、海马等。很早的时候研究者就发现:右半球损害造成的认知障碍更为严重,其中额叶的损害表现得尤为突出,尤其是额叶腹侧和内侧皮质的损害[1]。额叶主要与执行功能相关,包括抽象能力、概念形成、选择性记忆和认知过程转移能力。海马区主要和学习及记忆功能密切相关,海马区受损将会影响到对新知识的获得以及对已掌握知识的提取[2]。另外顶叶可能也参与某些认知活动[3]。近年来的研究表明,小脑可能也参与认知、情感等高级皮质功能[4],但是目前还缺乏肯定的证据。此外,与认知功能有关的神经递质包括:乙酰胆碱、多巴胺、去甲肾上腺素、五羟色胺、γ-氨基丁酸、谷氨酸等[5]。目前认为,脑损伤急性期神经递质变化对认知的影响可能是暂时的,而恢复期持续的认知障碍则同脑组织永久性损害,以及长期的脑内神经递质系统功能变化相关。

2 脑外伤和脑血管病所致认知障碍的共同机制

脑外伤和脑血管病虽有各自的损伤机制,但最后都会通过上述路径导致认知功能的损害,其中有些病理机制是相同的。例如,急性缺血性脑血管病时,在缺血部位发生一系列"缺血级联反应",表现为能量代谢障碍→兴奋性神经递质释放→自由基反应→钙过量内流→细胞死亡的过程。而在脑外伤急性期同样可以见到能量代谢障碍[6]、兴奋性氨基酸增加[7]、自由基产生[8]及钙离子内流[9]等。无论原发病为血管病变或外伤性损害,这些病理生理变化最终可导致神经细胞的死亡,破坏大脑的组织结构,可发生于皮质(如海马、颞叶、额叶等)或者影响到脑内的白质纤维,阻碍信号传递,进而导致认知功能障碍。目前的研究资料表明,神经递质除了参与脑损伤急性期的损害过程,恢复期的功能失常也对认知功能产生影响,其中主要包括多巴胺系统[10]、乙酰胆碱[11]、五羟色胺[12—13]及谷氨酸[14—15]等。

3 脑外伤和脑血管病所致认知障碍的不同机制

脑外伤和脑血管病所致认知障碍的机制不尽相同,其差异具体表现为以下几个方面:

3.1 年龄因素

脑外伤患者病前大部分可能为健康青年人[16],而血管性认知损害患者则多为老年人,并可能存在神经系统疾病或其他的危险因素[17],因而导致两类疾病患者群的认知功能基础状态存在差异。根据一些研究资料,在老年人中发生动脉粥样硬化、类淀粉样蛋白沉积等更为多见,这些变化可以引起血管炎症及氧化反应,导致脑血管疾病以及血管性认知障碍[18]。另外,老年人多合并高血压、糖尿病等慢性病,而这些疾病也是导致血管性认知障碍的因素。脑血管功能失调及血脑屏障作用的降低使得脑内微环境发生改变,从而使大脑认知相关结构(皮质、皮质下白质、海马等)更容易受到缺血缺氧的损害而导致认知障碍[19]。

3.2 脑外伤过程中某些特殊机制对认知功能的影响

3.2.1 物理因素:脑外伤主要的原因是由于外力的作用下使脑组织进行突然的加速和减速运动,而造成脑组织同周围结构的碰撞,或者由于惯性差异,导致组织结构的撕裂。在急性损害时,这种机械损害可能对脑组织产生加速或减速、旋转、对冲等机械力学作用。因此,TBI患者除了外伤局部的损害外,上述机械因素还会导致全脑的炎症性反应,更容易影响到皮质及皮质下联系纤维的功能。相比大部分脑血管疾病患者的脑部损害(蛛网膜下腔出血除外),TBI对脑组织的损害具有更为"泛化"的特点[20],这一特点可能是导致脑外伤患者认知障碍更加突出的主要原因。活体和体外研究发现[1],大脑皮质较纹状体对炎症损害反应更为敏感。相对于脑血管疾病,认知障碍在脑外伤住院患者中也更为普遍;即使是影像学上无任何改变的脑外伤,也会造成对全脑的影响而发生认知障碍[21],而中重度脑外伤患者几乎都会伴有认知障碍。单独发生在非认知相关区域程度较轻的脑血管事件对认知功能可能不造成任何影响。

3.2.2 弥漫性轴索损伤:弥漫性轴索损伤为TBI特有的一种病理过程,存在于75%的中重度TBI患者中[22]。TBI所致的弥漫性轴索损伤是在特殊的生物力学机制作用下(目前主要认为是瞬间旋转作用以及弥漫施力所产生的脑内剪应力所致),脑内发生的以神经轴索肿胀、断裂、轴缩球形成为特征的一系列病理生理变化。这种损害在急性期可能导致死亡或者意识障碍,但更为重要的是它可能启动长期的轴索变性过程,这种变化通常是隐匿的、进展性的,并且研究发现可能在TBI后多年仍然存在,影响脑内联系纤维的完整性和神经递质的正常传递[23—24],从而损害认知功能[25]。

3.2.3 正常颅压脑积水:正常颅压脑积水在脑外伤患者中常见,其机制不清,通过CT扫描诊断的正常颅压脑积水发生率占脑外伤患者的30%—86%[26]。由于它能够导致脑皮质及脑室周围白质和灰质的萎缩,影响到认知功能,因此为导致TBI后认知功能长期降低的重要原因之一。

3.3 脑血管疾病所致认知障碍的相关机制

3.3.1 血栓形成:近期的一些研究资料表明,凝血块形成和小血管梗死是血管性认知障碍的机制之一,高水平的纤维蛋白原、凝血酶原激活抑制因子以及凝血因子Ⅲ能够增加患血管性认知障碍的风险[27]。虽然房颤是公认的导致大面积栓塞的主要病因,但是也会引起小栓子脱落导致多病灶的脑血管疾病和认知障碍[28],或者加重血管性认知障碍患者的症状[29]。无症状性的脑缺血[30],通过损害脑内的白质,从而影响认知相关部位的联系纤维,最终导致认知功能的下降,如果发生

在海马，则能够选择性的引起记忆功能的下降[31]。常染色体显性遗传病合并皮下梗死和白质脑病（cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, CADASIL）通过引起皮质下的腔隙性梗死等机制损害认知功能，亦属于血管性认知损害的一类重要危险因素[32—33]，研究发现CADASIL患者海马的体积显著低于正常水平[34]。

3.3.2 出血：颅内出血同认知功能损害也有密切的关系，一项研究表明，自发性颅内出血同脑梗死一样，能够引起认知损害，并且其几率大致相同[35]。另外，蛛网膜下腔出血也会对认知造成损害。在对90例蛛网膜下腔出血患者发病后3个月进行的调查中发现，73%的患者存在认知损害，而迟发的脑梗死只能解释其中的31%—38%[36]。蛛网膜下腔出血导致的认知功能损害甚至在发病后5年还很明显[37]。近年来很多研究者又发现，微量的脑出血[38—39]也会影响到认知功能，并且可能导致长期的认知功能下降[38]，尤其发生在额叶和颞叶部位[40]。不伴有微量出血的血管性认知障碍，其认知功能恢复的可能性更大[41]。虽然目前机制尚不完全清楚，但有的学者研究发现，微量的出血可能影响胆碱能系统的功能从而导致认知功能下降，微量出血的这种作用独立于脑内白质损害范围及缺血性卒中两种因素[42]。

3.3.3 其他：遗传因素也可能是血管性认知障碍的形成机制之一。携带载脂蛋白E(ApoE)3以及4多态基因的卒中患者易发生认知障碍[43]，如果同时合并高血压或者糖尿病，其患血管性认知障碍的风险可能更高[44]，不过目前还没有确切证据。日本学者发现，血管性痴呆患者的超敏C反应蛋白以及肺炎衣原体抗体的浓度显著高于阿尔茨海默病患者，提示炎症可能在血管性认知障碍的形成中扮演着某种角色[45]。另外肥胖及运动过少也是血管性认知障碍尤其是中年患病人群的重要危险因素[46]。胰岛素抵抗、腹型肥胖、小血管内皮病变（例如血脑屏障的血管）以及慢性肾脏疾病都能加速血管性认知障碍的形成[18,47—48]。

总之，脑外伤和脑血管疾病所致的结构损害虽然有相似之处，但是脑外伤机械性损害更加突出，而血管性认知障碍形成过程中则以血管病变因素为主导。脑血管疾病导致的认知障碍大部分病因不能彻底根除，往往长期存在，并且随着年龄的增长会进一步加重，这些病因会对认知障碍造成长期影响，脑外伤患者发病年龄较轻[16]，患者生存期长，对康复目标要求较高，因此需要进行更积极的康复治疗。了解两种疾病所导致认知障碍病理机制的不同，有利于我们认识认知障碍的不同病因，制定有针对性的临床决策。

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