·综述·

高同型半胱氨酸血症与脑血管病研究进展

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摘要 脑血管病是高致残率、高复发率及高死亡率的疾病。近年来,高同型半胱氨酸(HHcy)作为脑血管病可控的危险因素逐渐受到重视。但Hcy是否是脑血管病的独立危险因素仍存在争议,降低Hcy是否可改善脑血管病患者的临床预后也存在不同的意见。本文综述了HHcy血症与脑血管病的研究进展。

关键词 同型半胱氨酸;脑卒中;脑出血

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脑血管病是发病率、致残率和病死率均高的疾病,包括缺血性和出血性卒中,缺血性卒中的发病率高于出血性卒中,占我国脑卒中的69.6%~70.8%。我国住院急性缺血性脑卒中患者发病后1年病死率为14.4%~15.4%,致死/致残率为33.4%~33.8%[1]。出血性脑卒中发病凶险,病情变化快,致死致残率高,超过70%的患者发生早期血肿扩大或累及脑室,3个月内的死亡率为20%~30%[2]。既往研究发现高同型半胱氨酸血症(hyperhomocysteinemia,HHcy)是冠状动脉粥样硬化、缺血性脑血管病的危险因素[3,4]。HHcy可损伤血管、诱发心脑血管疾病,同时与脑内微出血(cerebral microbleeds,CMB)密切相关[3,5]。Weili Zhang等[6]对1823例脑卒中患者随访了4.5年后发现,HHcy会增加脑卒中的死亡率和复发率。此外,合并HHcy的脑出血(intracerebral hemorrhage,ICH)患者的血肿体积往往更大[7],而血肿体积与ICH患者的预后相关。然而一些前瞻性、随机、安慰剂-对照试验并未显示使用叶酸降低Hcy会降低动脉粥样硬化、卒中的发生。因此,关于HHcy是否为卒中的危险因素及是否应该对脑卒中患者常规筛查Hcy存在争议[8]。所以,笔者对近几年的相关研究进展进行综述。

1 HHcy的代谢及影响因素

Hcy来源于饮食中摄取的蛋氨酸。蛋氨酸是人体必需的含硫氨基酸,在腺苷蛋氨酸合成酶的催化下生成腺苷蛋氨酸,随后在甲基转移酶作用下脱去甲基生成腺苷同型半胱氨酸,再经过腺苷同型半胱氨酸水解酶的水解作用脱去腺苷生成Hcy。蛋氨酸生成Hcy的途径有:再甲基化途径和转硫化途径[9]。在血液循环中,80%~90%Hcy以二硫键的形式与血浆白蛋白结合;10%~20%以Hcy二聚体或Hcy-半胱氨酸二硫化物的形式存在;约1%以游离巯基存在[10]。关于Hcy的正常参考范围,目前仍然存在争议,普遍认为:空腹状态下,血浆总Hcy的浓度(tHcy)正常范围为5~15 μmol/L。根据Hcy的浓度的不同,将HHcy分为轻、中、重3度。轻度:16~30 μmol/L;中度:31~100 μmol/L;重度:>100 μmol/L[11]。影响Hcy浓度的因素主要有:饮食中蛋氨酸过多:使Hcy生成过多;维生素B_{12}、维生素B_6、叶酸缺乏:使细胞内Hcy代谢受阻[12];代谢途径中的酶基因多态性或关键酶缺乏:使Hcy转化受到抑制;肾脏功能受损,使Hcy排泄受阻;其他如男性、高龄、高尿酸血症是Hcy水平升高的危险因素[13]。

2 HHcy与缺血性脑卒中

2.1 HHcy与缺血性脑卒中的发生风险

大量的研究证实,HHcy与缺血性卒中发生率相关[14,15]。He Y等[14]行Meta分析显示HHcy组的脑卒中发生风险是低Hcy组的1.69倍(95% *CI* 1.29-2.20)。另外有研究发现,与健康对照组相比,脑梗死患者的Hcy水平显着升高[16]。在中国人群中,Hcy在高血压的存在下进一步增加约70%的卒中风险[17]。并且tHcy与中国高血压患者首发卒中风险显著相关[15]。

2.2 HHcy与缺血性脑卒中复发风险

Anniwaer J等[18]进行的前瞻性研究发现,Hcy水平是复发性脑梗死的危险因素。一项Meta分析[14]共纳入了9项研究,其中2项研究报道了复发性卒中,研究结果显示高Hcy增加了76%的卒中复发风险。一项针对中国人群的研究,共纳入了1823例患者,随访了4.5年,在随访期间一共有347例患者复发卒中,在调整其他危险因素后,HHcy组的卒中复发风险是对照组的1.74倍[6]。然而,另外一项前瞻性研究[19]共纳入了1999年至2010年共11年的9522例卒中患者,研究表明,缺血性卒中早期的HHcy与缺血性卒中患者的卒中复发无关。Toole等[20]发现,降低3 μmol/L的Hcy可减少10%的复发性卒中。

2.3 HHcy与缺血性脑卒中预后

大量研究提示HHcy是缺血性脑卒中后短期、长期神经功能恶化和死亡率的独立预测因子[21-26]。Shi Z等[27]的研究纳入了3799例缺血性卒中患者并

随访了2年，在随访期间有233例死亡，调整其他危险因素后，血浆Hcy水平＞18.6 μmol/L的亚组患者死亡率是血浆Hcy水平≤10 μmol/L的亚组患者死亡率的1.61倍。进一步亚组分析显示，在大动脉粥样硬化卒中组发现血浆Hcy与死亡率有明显相关性（*HR*1.80；95%*CI*，1.05-3.07），但在小动脉闭塞性卒中的患者组无明显相关性（*HR*0.80；95%*CI*，0.30-2.12）。在中国急性缺血性卒中抗高血压试验（the China Antihypertensive Trial in Acute Ischemic Stroke，CATIS）[28]的急性缺血性卒中患者中，Hcy基线浓度与女性患者住院后3个月死亡和严重残疾有关，但Hcy基线浓度与男性患者住院3个月死亡和严重残疾无关。但此研究存在一定的不足，一些患者并非在入院24 h内测量Hcy，且血浆tHcy浓度仅在基线时记录1次，没有数据来检查tHcy变化与急性缺血性卒中预后之间的关系。此种现象需要进一步临床验证。

2.4 HHcy治疗与脑卒中

Huang T等[29]进行的Meta分析纳入19个RCT共47921例患者，研究发现，补充B族维生素对卒中患者有显著的保护作用（*HR*0.88；95%*CI*，0.82-0.95），但是对全因死亡率的风险没有影响。同样，另外一项研究[30]显示纳入2334例年龄为49~69岁的患者，共30个随机对照试验。基线Hcy血浆水平范围为9.8~50.3 μmol/L，叶酸剂量范围为0.8~40 mg/d，随访0.5~7年后，结果显示：叶酸补充剂可使卒中风险降低10%[*RR* 0.90 (95% *CI*，0.84-0.96，*P*=0.0020)]。

但也有研究发现，补充维生素、叶酸并不降低脑卒中的发生率。一项对13项随机对照试验的综述和荟萃分析中[31]，纳入39005例54~69岁的患者，平均随访时间为3.7年，研究叶酸降低Hcy对预防卒中的疗效，研究发现，在高心血管风险人群中，叶酸补充对卒中发生风险没有统计学意义（*RR*0.93；95%*CI*，0.85-1.03；*P*=0.16）。VITATOPS（VITAmins TO Prevent Stroke）试验[32]也得出相同结论，即给予维生素治疗不会影响卒中或血管性死亡的复合终点。最近的一项Cochrane系统评价显示[33]，就卒中而言，与安慰剂相比，单独或联合给予维生素B_6、B_9或B_{12}补充剂的方式降低Hcy的效果差异很小。与依那普利加叶酸相比，叶酸对卒中有不确定的影响，大约143例（95%*CI*，85-428）需要服用叶酸5.4年才可预防1次中风。

鉴于以上研究，目前还没有足够的证据表明降低Hcy浓度可减少心血管疾病、卒中和全因死亡率，美国心脏协会/美国卒中协会目前的指南[34]建议不要对近期缺血性卒中或TIA患者Hcy水平进行常规筛查（III级推荐，C级证据）。虽然没有随机、安慰剂-对照研究表明Hcy降低疗法可减少缺血性卒中复发，但仍建议缺血性卒中和HHcy血症的脑卒中和TIA患者补充叶酸、维生素B_6和维生素B_{12}（III级推荐，B级证据）。

2.5 HHcy在缺血性脑卒中的发病机制

目前HHcy导致缺血性卒中的病理机制现在尚无定论[35]。大多数研究集中在HHcy致动脉粥样硬化、炎性应激等传统机制，近年来，对Hcy基因多态性和表观遗传调控机制的研究逐渐增多。

2.5.1 HHcy致脑血管病的传统机制 目前研究显示，Hcy是动脉粥样硬化的独立危险因素。Hcy导致并加速动脉粥样硬化的机制多样且复杂，主要包括：①内皮损伤及功能障碍：Hcy可以导致血管内皮的损伤，是血管疾病发展初始和重要事件。Hcy介导的内皮毒性损伤内皮、功能障碍主要涉及活性氧（reactive oxygen species，ROS）的大量产生。氧化自由基会导致内皮来源的一氧化氮生物利用度减低，从而使内皮细胞不能对各种刺激做出反应[10]。②影响平滑肌细胞的增殖：血管平滑肌细胞可通过增强小凹蛋白表达等几种途径向内膜转移增殖。③炎症因子表达增强：Hcy可以促进白细胞介素-8（IL-8）、单核巨噬细胞趋化因子（monocyte chemoattractant protein，MCP）-1及其受体的表达和分泌，还可上调血管细胞粘附分子（vascular cell adhesion molecule，VCAM）等途径促进动脉粥样硬化的发生发展。④氧化应激：Hcy不仅可使过氧化氢（H_2O_2）等ROS的生成，还可抑制细胞外超氧化物歧化酶的表达和分泌。

2.5.2 Hcy的基因多态性 血浆Hcy水平与代谢途径中酶的活性下降有关，具有很明显的遗传倾向性[36]。①目前研究较多是MTHFR基因，此基因存在10余种突变，其中最常见的677 C→T、1298 A→C两个位点的突变[37,38]；②CBS基因，CBS基因突变研究较多的是T833→C、844ins68、T27796→C以及G919→A；③MS基因，MS基因最常见的突变是A275G突变。Hcy相关基因与卒中风险是否相关仍需要大样本量的研究[39]。

2.5.3 Hcy的表观遗传调控机制 组蛋白修饰、DNA甲基化、染色质重组和非编码RNA的调控是决定表观遗传学过程的主要因素。这4个水平之间相互作用，但其互相关系及如何共同调节染色质结构还有待进一步研究。研究表明Hcy可通过表观遗传调控机制在卒中的病理生理机制中发挥很重要的作用[40,41]。Baccarelli等[42]证实，缺血性卒中患者与健康对照者相比，整个基因组DNA甲基化水平明显降低。另外有研究表明组蛋白修饰、非编码RNA和核小体重塑等均参加了Hcy相关卒中发生的过程，但是具体机制有待进一步深入研究[41]。

3 HHcy与ICH

ICH是死亡率最高的卒中类型。关于Hcy和ICH之间的关联仍然存在争议。一项关于日本人群的研究结果表明[43]，HHcy不会增加出血性卒中的风险。He Y等[14]进行的Meta分析显示，Hcy水平升高的患者出血性卒中的风险增加，但没有达到统计学意义（*RR*1.65；95%*CI*，0.61-4.45），此荟萃分析纳入的出血性卒中的研究数量较少，无法得出可靠的结论。另外研究发现ICH患者的Hcy浓度高于健康对照组，提示血浆Hcy水平与ICH存在着潜在的机制[14,44]。Wang BR[5]发现血清Hcy水平和大动脉粥样硬化引起急性卒中患者的脑微出血相关，血清Hcy水平也许是改善脑微出血临床结局的一个潜在靶点。还有研究提示HHcy的丘脑出血患者和低血浆Hcy浓度的丘脑出血患者相比，HHcy患者的血肿体积较大[7]。

4 存在的问题与展望

最近的研究发现HHcy会增加脑卒中发生率和复发率[15,18]，

但是否应常规筛查HHcy血症或用叶酸和B族维生素治疗仍然存在争议[8]。此外，血浆Hcy的中度升高最常见，会发生在5%~7%的人群中[45,46]。老年人中HHcy普遍存在，此外，老年人维生素B_{12}缺乏症且伴有HHcy的患病率很高，其中约40%患有卒中或短暂性脑缺血发作（transient ischemic attack，TIA）。人口老龄化的增加及老年人更易发生脑卒中的事实可能会改变对筛查和治疗的态度[6]。对于Hcy是否会增加ICH的发生率和加重临床结果的不良影响，仍然存在很大争议。期待新的随机、安慰剂-对照试验来帮助解决这个争议。

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