电子、语音版

·综述·

蛛网膜下腔出血的脑损伤机制及相关生物标志物研究进展

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摘　要：蛛网膜下腔出血（SAH）是一种严重的急性出血性脑卒中，具有极高的致死率和致残率。出血后发生脑损伤的机制主要包括早期脑损伤和迟发性脑缺血，最终会导致预后不良。目前，治疗并减轻脑损伤的措施有限。在此，笔者回顾了SAH动物模型及SAH后脑损伤的病理机制，并总结了相关的生物标志物在脑损伤及预后不良中的作用，以期为SAH的药物研发及临床治疗方案制订提供思路。　[国际神经病学神经外科学杂志, 2023, 50(3): 51-59]

关键词：蛛网膜下腔出血；动物模型；早期脑损伤；迟发性脑缺血；生物标志物

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Research advances in the mechanism of brain injury and related biomarkers in spontaneous subarachnoid hemorrhage

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Abstract: Spontaneous subarachnoid hemorrhage (SAH) is a severe acute hemorrhagic stroke with extremely high mortality and disability rates. The main mechanisms of brain injury after hemorrhage include early brain injury and delayed cerebral ischemia, which will eventually lead to poor prognosis. At present, there are limited measures to treat and alleviate brain injury. This article reviews the animal model of SAH and the pathological mechanism of brain injury after SAH and summarizes the role of related biomarkers in brain injury and poor prognosis, in order to provide ideas for developing drugs and clinical treatment regimens for SAH.[Journal of International Neurology and Neurosurgery, 2023, 50(3): 51-59]

Keywords: subarachnoid hemorrhage; animal model; early brain injury; delayed cerebral ischemia; biomarker

蛛网膜下腔出血（subarachnoid hemorrhage, SAH）是颅内血管破裂导致血液流至蛛网膜下腔的一种急性出血性脑血管疾病，85%是由颅内动脉瘤破裂所致[1]。尽管医学诊疗手段已获得较大进展，但目前其致死率和致残率仍然很高。预后不良与SAH后的脑损伤包括早期脑损伤（early brain injury, EBI）和迟发性脑缺血（delayed cerebral ischaemia, DCI）密切相关，因此，探讨SAH后脑损伤的病理机制并寻求相关措施来改善预后具有极大的临床意义。本文就SAH的动物模型、SAH后脑损伤的病理机制及相关生物标志物的研究进展作如下综述。

1　SAH动物模型

当前最常用SAH模型有单次注血模型、二次注血模型和血管内穿刺模型。单次注血模型是从股动脉抽取一定量的自体血注入枕大池，最早由Delgado等[2]报道。二次注血模型则是在单次注血模型的基础上，间隔48 h后再次向枕大池注入自体动脉血，较单次注血模型成功率

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更高,导致脑血管痉挛的概率也更高。上述两种模型操作简单、出血量可控、可重复性高,但有可能损伤脑干,且不能准确模拟人类SAH的发病过程。血管内穿刺模型是借鉴了线栓法大脑中动脉闭塞模型的方法建立的。具体操作是在显微镜下游离结扎颈外动脉,将穿刺线由颈外动脉进入,往前推送到达大脑中动脉,并在此穿破血管壁。这种方法死亡率较高[3],出血程度随机性较大,但能够较真实地模拟颅内动脉破裂导致的SAH。总之,SAH动物模型为SAH病理机制的研究及后续相关治疗方案研发提供了便利,但各有不足之处,仍需在今后的实验中不断改进。

2　SAH后的脑损伤

目前人们普遍把SAH后脑损伤按发生时间分为EBI和DCI两个阶段。EBI发生在前72 h。当血液在高动脉压下涌入蛛网膜下腔时,颅内压(intracranial pressure,ICP)会升高。血液及其分解产物还可能因脑脊液流动受阻而进一步导致ICP升高,从而导致脑积水。ICP的急剧升高导致脑灌注压和脑血流量显著降低进而出现全脑缺血。在此基础上进一步发生多种复杂病理反应过程,包括神经炎症、微血栓形成、皮质扩散性去极化、血脑屏障(blood brain barrier, BBB)的完整性破坏、微血管功能障碍及大脑血管痉挛[4]。这些病理事件之间可能相互促进,共同作用,为DCI及不良预后的发展奠定了基础。DCI临床上是指SAH患者出现不能归因于其他原因的任何神经功能恶化(局灶性神经功能缺损或格拉斯哥昏迷评分下降大于等于2分)持续时间超过1 h[5]。约30%的SAH患者会发生DCI,通常发生在动脉瘤破裂后第3~14天[6]。尽管脑损伤过程被人为划分为两个阶段,但事实上EBI与DCI之间可能是一种因果关系,其发生机制都与神经炎症、血管功能失调、BBB破坏、微血栓形成、皮质扩散性去极化有关。

2.1　神经炎症及相关标志物

SAH后发生的神经炎症是一种无菌性炎症。动脉瘤破裂后,蛛网膜下腔中的红细胞会发生降解,释放出大量具有生物活性和潜在毒性的分子,包括血红蛋白、高铁血红蛋白、胆红素、纤维蛋白原等[7-11]。释放的这些内源性分子可以作为损伤相关分子模式(damage-associated molecular patterns, DAMPs)与小胶质细胞等免疫细胞表面的模式识别受体(pattern recognition receptors, PRRs)结合。Toll样受体4(TLR4)就是这样一种PRR,它与DCI的发生和不良预后相关[9,12]。PRRs的激活可进一步导致下游炎症信号级联反应的激活,包括髓样分化因子88(MyD88)、β干扰素TIR结构域衔接蛋白(TRIF)、丝裂原活化蛋白激酶(MAPK)和核因子-κB(NF-κB)信号转导途径的激活,这些信号转导途径都参与了促炎基因的转录[10,12-13]。小胶质细胞作为中枢神经系统(central nervous system,CNS)的主要免疫细胞,被激活后极化为促炎表型(M1型)并释放促炎细胞因子。在SAH动物模型中,小胶质细胞激活和促炎细胞因子表达一直持续到第21天,并且与长期感觉运动障碍有关[14]。实验中耗尽小胶质细胞还可以减少小鼠的血管痉挛和神经细胞凋亡[12]。虽然大多数研究都集中关注小胶质细胞激活和释放促炎因子的不利影响,但众所周知,小胶质细胞还可以极化为抗炎表型(M2型)。促进这些小胶质细胞向抗炎表型的激活可能会带来神经保护作用,这可能也将是SAH早期治疗策略的探索方向[15]。

除了血红蛋白及其衍生物外,还有其他多种DAMP参与了SAH神经炎症的启动与维持,包括高迁移率族蛋白B1(high-mobility group box 1, HMGB1)、S100钙结合蛋白B(S100 calcium binding protein B, S100B)、细胞外基质成分、IL-1α、IL-33、线粒体DNA和热休克蛋白[16]。近年来,关于HMGB1在SAH后发挥作用的证据不断增多。2009年Nakahara等[17]首次发现动脉瘤性蛛网膜下腔出血(aneurysmal subarachnoid hemorrhage, aSAH)后患者脑脊液中HMGB1的释放,预后不佳的患者脑脊液中HMGB1水平更高,并且HMGB1水平与肿瘤坏死因子-α(TNF-α)、白细胞介素-6(IL-6)和IL-8相关,表明HMGB1在SAH神经炎症的维持中不可或缺的作用。King等[18]还发现脑脊液HMGB1水平升高与SAH患者更高的Hunt-Hess分级及更差的功能预后密切相关。随后Zhu等[19]评估了SAH患者血浆中的HMGB1水平,并证明与脑血管痉挛、不良功能预后及1年死亡率相关,强调了入院时血浆HMGB1测定的预测价值。S100B是一种钙结合蛋白,在大脑中主要由星形胶质细胞表达并发挥多种细胞内作用[20-21]。病理情况下,例如在神经退行性疾病或炎症性脑病中,坏死和受损的细胞被动释放S100B导致浓度升高。而在较高浓度下,S100B会表现为损伤相关分子模式(DAMPs),与晚期糖基化终末产物受体(RAGE)结合产生神经毒性作用,促进神经元死亡[21]。Kay等[22]在研究载脂蛋白时,偶然发现SAH后脑脊液S100B水平升高。对aSAH患者脑脊液的连续测定显示,S100B水平升高与3个月临床结果密切相关[23]。一项前瞻性队列研究发现15 d内血浆平均S100B水平升高与脑血管痉挛导致的迟发性脑缺血有关,并且可作为1年后不良临床结局的预测因子,截断值为0.23 μg/L,敏感性为91%,特异性为90%[24]。

此外,IL-1、IL-6、TNF-α等促炎细胞因子也已被证明在SAH后的脑脊液和血清中上调[25-26]。促炎细胞因子可通过触发细胞凋亡途径、干扰内源性血管扩张剂和血管收缩剂的平衡、激活导致微血栓形成的凝血因子以及上调细胞黏附分子并募集外周免疫细胞来加剧脑损伤[8]。尤其是IL-1会增加BBB通透性,增强神经胶质介导的神经毒性,并在实验模型中促进SAH后的缺血性变

化[27-29]。另外,巨噬细胞迁移抑制因子(macrophage migration inhibitory factor, MIF),一种同源三聚体蛋白,也已被证明可作为促炎细胞因子激活CNS中的炎症反应。在实验研究中,MIF从活化的胶质细胞中释放出来,进一步激活星形胶质细胞释放炎症介质,通过促进神经元细胞死亡导致脑损伤[30-31]。血清MIF浓度与SAH患者的严重程度相关,且是患者预后不良的预测因子[32-33]。细胞因子和趋化因子的初始释放发生在CNS的常驻细胞(例如小胶质细胞)中,但随后外周免疫细胞的浸润进一步驱动蛛网膜下腔和脑实质内促炎细胞因子的产生。

SAH后神经炎症发展也与内皮细胞、血小板和白细胞表面的细胞黏附分子表达增加有关。细胞黏附分子(如细胞间黏附分子-1)和细胞外基质重塑蛋白(如基质金属蛋白酶-9)的表达增加可导致BBB破坏和通透性增加[10,34]。这促进了中性粒细胞、单核/巨噬细胞和淋巴细胞等外周免疫细胞跨血脑屏障迁移到蛛网膜下腔。在一些研究中观察到SAH后几小时中性粒细胞和巨噬细胞进入蛛网膜下腔并进一步促进炎症发展[35]。另一项研究发现,中性粒细胞并不直接侵入蛛网膜下腔,但通过分泌细胞因子参与CNS的免疫炎症反应[36]。在大鼠模型中,使用中性粒细胞抗体损耗中性粒细胞,可以抑制白细胞与软脑膜血管的黏附,最终改善神经预后[37],这都表明中性粒细胞在SAH的炎症发展及不良预后中起重要作用。其他研究也得出了类似的结论[38-39]。此外,血清中性粒细胞淋巴细胞比率也被发现与DCI相关,可作为神经功能预后不良的标志物[40-41],但其在EBI中的作用尚不清楚。显然,各种免疫细胞之间的复杂相互作用值得进一步研究。

2.2　脑血管功能失调

几十年来,脑血管功能失调一直SAH的研究焦点之一,关注点主要在较大的脑表面血管。从机制上,这种血管功能失调与蛛网膜下腔中存在的血管活性血液降解产物、内源性血管扩张剂[如一氧化氮(NO)]和血管收缩剂[如内皮素-1(Endothelin-1, ET-1)]的产生不平衡以及炎症有关[4]。NO是调节血管平滑肌张力的关键内皮细胞衍生因子之一,它通过增加血管平滑肌细胞中环磷酸鸟苷(cyclic guanine monophosphate, cGMP)的水平引起血管扩张和脑血流量增加[42-43]。SAH后NO水平下降通常发生在发病后30 min和发病后第4~7天[44],这可能是与血红蛋白结合或炎症所导致的。此外,正常情况下剪切力通过内皮型一氧化氮合酶诱导动脉扩张,但这一途径在SAH后受损[45],据报道,在SAH后7 d,一氧化氮合酶转录表达明显减少[46]。此外,内皮型一氧化氮合酶的内源性抑制物,如非对称二甲基精氨酸和蛋白激酶C被发现在SAH后上调[46]。临床和动物实验表明,血管痉挛可以通过提供外源性NO供体(如硝普钠或硝酸甘油)来改善[47-48]。然而,这些药物的全身不良反应(主要是低血压)使其不适合在临床中常规全身给药。ET-1是最有效的内源性血管收缩剂之一,由内皮细胞受到缺血损伤和氧合血红蛋白的刺激产生。研究表明血管痉挛患者脑脊液中的ET-1水平高于健康受试者,ET-1水平升高与缺血性症状的发生有关[49-50]。另一项研究发现,尽管ET-1水平在DCI患者中更高但与血管造影显示的脑血管痉挛无关[51],这表明ET-1可能是缺血性脑损伤的标志物,而不是血管痉挛。

脑血管痉挛被定义为在计算机体层血管成像(CTA)、磁共振血管成像(MRA)或数字减影血管造影(DSA)等放射学检查中观察到的大脑动脉狭窄[5],血管造影显示高达70%的患者在SAH后发生血管痉挛[52],但DCI只在30%的患者中观察到,且不总发生在血管造影血管痉挛的血管分布范围[53-54]。目前唯一被美国食品药品监督管理局批准的预防SAH后DCI的药物尼莫地平对血管造影血管痉挛没有明显改善[55-56]。此外,克拉生坦作为一种选择性内皮素受体A拮抗剂,可以降低脑血管痉挛的发病率,但对长期功能预后没有影响[57]。这些证据充分表明血管痉挛不是导致SAH后DCI和预后不良的唯一因素,需要进一步了解SAH后脑血管功能失调的机制并确定治疗靶点。

除了较大的脑表面血管发生血管造影血管痉挛外,较小的脑实质微血管结构也可表现出改变。越来越多的证据表明,微血管功能障碍与EBI和DCI有关[58-59]。与血管造影血管痉挛相比,微血管功能障碍在临床上不能通过血管造影或经颅多普勒超声轻易发现。大脑微血管系统内的各种细胞类型,包括内皮细胞、周细胞和血管平滑肌细胞,与周围的神经元和神经胶质细胞不断交流,共同构成一个功能性神经血管单元。在正常情况下,这些不同的细胞之间信号交流导致微血管张力和组织灌注的变化,以应对神经元的能量需求[58,60],这个过程被称为神经血管耦合。突触释放的谷氨酸激活神经元上的N-甲基-D-天冬氨酸受体(NMDAR)以及星形胶质细胞上的代谢谷氨酸受体(mGluR)并将信号传递给动脉中的血管平滑肌细胞,这两种受体都通过增加细胞Ca^{2+}浓度来发挥作用。在神经元中,Ca^{2+}浓度升高激活一氧化氮合酶产生NO,星形细胞内Ca^{2+}浓度升高激活磷脂酶A2(PLA2),产生花生四烯酸(AA),从而生成环氧二十碳三烯酸(EET)和前列腺素E2(PGE2),两者都能促进血管扩张和增加血流,以适应增加的代谢需求[61]。而在SAH中,溶血会导致血管周围K^+浓度增加和NO减少[62],此外脑脊液中的血液降解产物诱发实质小动脉周围的星形胶质细胞终足的自发Ca^{2+}振荡振幅增大,导致细胞外和血管周围K^+激增[62]。因此,SAH后,兴奋的神经元所诱导的谷氨酸释放导致血管周围K^+浓度过高和清除障碍,从而导致微小动

脉血管平滑肌细胞去极化,诱发血管收缩或神经血管耦合的病理逆转[63]。在大鼠和小鼠SAH模型中,任何神经元或代谢激活,如感觉刺激、CO_2增加和pH值下降,都会导致脑实质动脉收缩和脑血流灌注相对不足,造成进一步脑损伤[59]。Friedrich等[58]的研究结果显示,SAH后72 h内超过70%的小动脉收缩,且更小的动脉收缩程度更大。其他研究中也有类似的发现,并描述为"珍珠线"样的小动脉收缩[64-65]。SAH后还可以观察到脑微血管内的其他一些结构和细胞变化。研究表明,微绒毛从血管壁生成并向管腔伸出形成气泡样结构,这种结构可以从基底层剥离并阻塞管腔[59]。除了直接影响血流外,这些变化还会引发血小板和白细胞的黏附,促进微血栓形成和神经炎症。周细胞在SAH中也对血管张力和脑血流量改变也起重要作用。在大鼠SAH模型中,渗漏脑实质的血红蛋白可通过抑制NO/cGMP信号通路来诱导周细胞α-平滑肌肌动蛋白表型转化,从而导致微血管收缩[66]。此外星形胶质细胞终足肿胀也会进一步减少血流[59]。总之,神经血管单元内的多种细胞类型共同驱动了SAH后的微血管功能障碍。

2.3　血脑屏障破坏与脑水肿

血脑屏障(BBB)是大脑自我保护的天然屏障,内皮细胞之间紧密连接的存在阻止了血液中的蛋白质和细胞成分进入脑实质,供了一个相对隔离的脑内环境。SAH会破坏BBB的完整性。研究发现BBB损伤最早可在10 min内出现,在24 h内达到高峰,并可持续到SAH后的第7天[63]。在实验性SAH后观察到内源性蛋白质和注射染料的渗漏[64],临床SAH患者在DSA检查或介入治疗后也经常能发现造影剂外渗到蛛网膜下腔。这些现象都印证了SAH导致BBB破坏和通透性增加。从机制上讲,BBB完整性的丧失与基质金属蛋白酶等降解紧密连接和基底层的蛋白酶上调有关。基质金属蛋白酶-9(matrix metalloproteinases-9, MMP-9)可能是SAH细胞外基质蛋白降解和紧密连接破坏的关键参与者[67]。SAH中MMP-9的来源尚不清楚,此前在缺血性卒中模型发现脑缺血急性期24 h内MMP-9主要来源于中央缺血区的内皮细胞,7~14 d主要出现在梗死周围皮质的星形胶质细胞和神经元中[68]。最近的研究发现,SAH后MMP-9的增加主要来自反应性星形胶质细胞,N-myc下游调节基因2/镁依赖性蛋白磷酸酶1A(NDRG2/PPM1A)信号是其产生的关键开关[69],这可能是新的BBB保护治疗途径。MMP-9还可以通过激活促炎信号和凝血因子来驱动神经炎症,触发血栓性炎症和神经毒性的正反馈回路[70]。在临床研究中也确实观察到SAH患者血浆和脑脊液中MMP-9增加,并且是预测DCI及功能预后不良的标志物[70-72]。

脑水肿的机制普遍被认为有两种,一是细胞内水和离子调节失衡所致细胞毒性水肿,第二种是BBB通透性增加所致的血管源性水肿。在分子水平上,脑水肿可能与水通道蛋白-4、MMP-9、磺酰脲受体1-瞬时受体电位M4型(SUR1-TRPM4)阳离子通道、血管内皮生长因子、缓激肽有关[67]。目前临床上已证明脑水肿是SAH后死亡和预后不良的危险因素[73],也是认知功能障碍的预测因素[74]。脑水肿在宏观影像学上可表现为大脑半球肿胀,脑沟变浅。Ahn等[75]通过设计早期脑水肿评分(subarachnoid hemorrhage early brain edema score, SEBES)评估SAH后早期水肿,提示SEBES可能是EBI的替代指标和DCI的预测指标。最近Yuan等[76]使用人工智能算法测量选择性脑沟容积(selective sulcal volume, SSV)评估全脑水肿,发现72 h内的最低SSV是不良预后的预测因素。

2.4　扩散性去极化

扩散性去极化(spreading depolarization, SD)是中枢神经系统灰质中突然的、持续的大规模去极化波的总称,使用硬膜下电极检测表现为缓慢移动和传播的波,由神经元跨膜离子梯度崩溃诱发[77]。在这种去极化的基础上,伴随着细胞内外离子稳态失衡、钠和水进入去极化的细胞导致细胞毒性水肿和坏死以及大量神经递质释放,在严重的情况下,SD可能引起扩散性抑制,此时表现为大脑中自发电活动的丧失[78]。谷氨酸大量释放后通过与N-甲基-D-天冬氨酸受体(NMDAR)、α-氨基-3-羟基-5-甲基-4-异恶唑丙酸受体(AMPA)和红藻氨酸受体(KAR)结合,导致过度刺激和细胞死亡,从而诱导神经毒性。除了神经递质引起的神经毒性外,局部脑血流量也会发生与SD相关的变化。短暂诱发SD可升高局部脑血流量,导致扩散性充血[77]。然而,尽管局部脑血流量升高,但在SD过程中脑耗氧量也会增加,充血不能完全补充代谢增加所需要的氧[79],因此在大多数皮质毛细血管远端供应区域可能会出现组织缺氧。而SD如果持续存在,扩散性充血则可能逆转为扩散性缺血。

目前已提出SAH后SD的潜在机制:SAH后,血凝块覆盖在脑表面,改变皮质微环境和血管反应性,血液成分降解引起细胞外K^+升高和NO降低,导致SD过程中细胞外离子变化的净效应从血管扩张转变为血管收缩[80];此外,升高的K^+可能导致星形胶质细胞和血管平滑肌细胞内Ca^{2+}储存的增加,这可能进一步增强Ca^{2+}释放时的血管收缩反应[81],此时就出现脑组织灌注减少和神经血管耦合逆转,随后发生扩散性缺血。因此,SAH后SD的发生和血管收缩剂的持续释放建立了一个恶性循环,其中SD维持血管收缩和缺血,同时缺血可持续诱发SD,进一步加重脑损伤。

1980年,Hubschmann等[82]首次在猫模型中证明SAH后存在SD。多年后,Dreier等[83]在人类SAH患者中证实了SD。这项前瞻性多中心研究共纳入18例SAH患者,通

过硬膜下植入皮层电极并监测脑电图的方式在13例(72%)患者中观察到了SD,而且还发现SD与DCI的发展密切相关,且对DCI具有很高的预测价值[83]。随后另一项研究也表明,大多数SAH患者存在SD,并且可以在无血管痉挛的情况下发生[84]。鉴于SAH后SD的高发病率及其预测DCI发展的作用,目前许多研究致力于靶向干预SD的发展以治疗SAH。Carlson等[85]发表了一项用麻醉剂氯胺酮抑制创伤性脑损伤和aSAH患者SD的前瞻性队列研究。最近还有一项研究聚焦于一种N-甲基-D-天冬氨酸受体拮抗剂美金刚,它可能是一种有希望的替代药物[86]。总之,目前针对的SD干预措施似乎都有较好的效果,未来需要进一步研究以确定最适宜的治疗方法。

2.5　微血栓形成

SAH后脑损伤的另一个新机制是微血栓的形成。微血栓形成会在整个大脑中产生相应的微梗死灶,从而对神经功能产生有害影响。许多研究表明,SAH后凝血和纤溶级联反应都发生了变化[44,58,87]。这可能与微小动脉痉挛密切相关,因为它创造了一个促凝环境。小动脉血管收缩后,血栓形成的三要素包括血流瘀滞、血液高凝状态和血管内膜损伤都有可能出现。此外,尼莫地平已被证明影响SAH后的纤维蛋白溶解活性,潜在促进大脑内微血栓的分解[88],这可能与其抑制小动脉血管收缩的能力共同构成该药物的治疗机制。

SAH后微血栓形成在1983年的一项尸检研究中首次被观察到[89],之后又在动物模型和人体上进行了深入研究。在小鼠模型中发现,SAH引发小动脉收缩及微血栓形成,可能进一步导致神经元凋亡,其机制可能与NO降低及P-选择素增加有关[90]。研究发现,在2个大脑半球都能观察到微血栓,因此推测它不仅仅由动脉瘤破裂部位的内皮损伤所导致[90-91]。从发生时机上看,SAH患者的微血栓形成在EBI和DCI都存在,且更高的血小板活化水平与患者DCI发展相关[92-93]。此外,一些研究显示微血栓形成与SAH小鼠长期认知功能障碍相关[94],总之,DCI的神经功能障碍可能是微血栓形成的结果,微血栓形成与认知功能障碍之间的关系值得进一步研究。

微血栓形成与DCI及预后不良的相关性也使之成为潜在的治疗靶点。他汀类药物具有修复血管内皮的作用,一些关于他汀类药物治疗SAH的研究显示其能减少血管痉挛的发生,但对DCI的发生和死亡率没有影响[95]。低剂量普通肝素在治疗SAH的临床试验显示了良好的安全性,且在不改变血管造影血管痉挛的情况下减少了DCI,并改善了认知功能结果[96-97]。

总之,SAH的致死率和致残率仍然很高,这与SAH后所发生的神经炎症、脑血管系统失调、血脑屏障受损、皮扩散性去极化、微血栓形成等一系列病理变化紧密相关。这些病理过程之间通过复杂的相互作用共同引发了EBI并促进随后DCI的发展。总结探讨脑损伤的病理机制并进一步寻求相关的治疗靶点对于避免预后不良的发生具有十分重大的意义。确定可靠的诊断或评估并发症及预后的标志物可能是当前的首要目标,这有助于在早期更客观地识别那些病情更严重的患者,并尽早积极地采取相应的治疗措施。目前关于SAH脑损伤标志物的研究有很多,但尚无理想的标志物用于临床。理想的生物标志物应该与SAH的脑损伤机制密切相关,且便于在发病早期检测或观察。因此,SAH的脑损伤机制及相关生物标志物仍需进一步深入研究。

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