

慢性硬膜下血肿形成及复发机制的研究进展

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摘 要

慢性硬膜下血肿(chronic subdural hematoma, cSDH)是常见的神经外科疾病, 多见于老年人。血肿的进展原因、转化为慢性的过程有其复杂的病理生理机制, 并与治疗效果息息相关。目前, 慢性硬膜下血肿的主要治疗方法是钻孔引流术, 但存在需要再次手术的复发风险, 目前术后复发率约9%~37%。目前所认为的血肿复发的主要原因主要是钻孔术后血肿包膜依旧存在, 血肿形成的病理生理机制并未被阻断。为降低术后复发率, 目前对潜在病理生理学机制的理解已用于新的治疗方法——脑膜中动脉栓塞术(middle meningeal artery embolization, MMAE)。还需要大量研究以确定脑膜中动脉栓塞术是否能成功停止血肿进展过程, 从而控制和缓解cSDH。本文就cSDH发生发展过程中的血管生成、炎症反应、纤溶亢进等关键过程以及cSDH复发机制和降低复发率的手术方式进行综述。

关键词

慢性硬膜下血肿, 机制, 复发, 研究进展

Progress in the Study of the Mechanism of Formation and Recurrence of Chronic Subdural Hematoma

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Abstract

Chronic subdural hematoma (cSDH) is a common neurosurgical disease, mostly seen in the elderly. The progressive, chronic course of the disease has its own complex pathophysiological mechanisms and is closely related to the outcome of treatment. Currently, the main treatment for chronic subdural hematomas is drilling and drainage, but there is a risk of recurrence requiring reoperation, with current recurrence rates of approximately 9%~37%. The main reason for hematoma recurrence is that the hematoma envelope remains after drilling, and the pathophysiological mechanism of hematoma formation has not been blocked. To reduce the rate of postoperative recurrence, an understanding of the underlying pathophysiological mechanisms has been used in a new therapeutic approach, middle meningeal artery embolization (MMAE). Numerous studies are needed to determine whether MMAE is successful in stopping the process of hematoma generation and thus controlling and alleviating cSDH. This article provides a review of the key processes of angiogenesis, inflammatory response, and hyperfibrinolysis in the development of cSDH, as well as the mechanisms of recurrence of cSDH and new surgical approaches to reduce the recurrence rate.

Keywords

Chronic Subdural Hematomas, Machine Processed, Recurrence, Research Progress

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1. 引言

慢性硬膜下血肿(chronic subdural hematoma, cSDH)是一种起病隐匿的颅内出血性疾病,大部分在患者受到轻微头部外伤后约3周左右,未完全吸收的出血转化为慢性血肿。cSDH临床表现多变,患者可表现为认知障碍、步态障碍、肢体无力、顽固性头痛等,甚至有些患者可表现为昏迷、癫痫发作。研究发现部分cSDH患者没有明确的临床表现,更多见的是整体精神状态和神经功能的降低[1],其症状的多变是由于血肿体积变化导致颅内占位效应引起的[2][3]。cSDH仅凭临床症状容易误诊、漏诊,完善CT、MRI等影像学检查可明确诊断,CT及MRI均表现为新月形影。

据统计,该病的发病率为1.72~20.60/10万人/年,预计到2030年cSDH将会成为神经外科最常见的疾病之一[4]。cSDH的平均患病年龄约为66~74岁[5],随着我国社会人口老龄化加剧以及近年来抗血小板和抗凝药物的广泛使用,cSDH的发病率和病死率逐年上升[6],约20%的患者失去自理能力,需要长期护理[7]。目前有共识的cSDH的一线治疗方案为硬膜下钻孔引流术,目前手术的术后复发率约为5%~30%。复发后需进行二次手术,二次手术影响了患者的生活质量,增加了患者的住院时长及经济负担并且有可能导致不良预后[8]。近年来多种研究对血肿形成及复发的机制产生了兴趣。许多研究希望通过对于血肿形成及复发机制的研究降低cSDH术后复发率。本文就cSDH发生发展过程中的血管生成、炎症反应、纤溶亢进等关键过程以及cSDH复发机制和降低复发率的手术方式进行综述。

2. 慢性硬膜下血肿的形成机制

2.1. 血肿形成

目前普遍认同的血肿发生机制是桥静脉牵拉出血机制,当伴有脑萎缩的老年患者受到轻微头部外伤

后,硬膜下潜在腔隙增宽,桥静脉原有张力改变,受到牵拉,导致出血[9][10],血液进入缺乏紧密连接的硬脑膜边界细胞层形成硬膜下血肿[11]。然而在临床中可以观察到并非所有的急性硬膜下血肿都会转化为慢性血肿。因此慢性血肿的形成不仅仅是外伤导致的其中还有更为复杂的病理生理机制。

2.2. 血肿包膜形成机制

在血肿形成后,一种类似于伤口愈合的反应过程开始,当血液聚集在硬脑膜边缘细胞层后,在血肿外逐渐形成新膜包裹血肿,研究发现慢性硬膜下血肿液中 I 型(PICP)和 III 型(PIIINP)胶原前肽明显升高,并且其升高与时间相关,其会持续升高约 3 个月,这时胶原蛋白的合成大于分解,血肿周围产生新生包膜,且包膜不断纤维化趋于成熟[12][13]。有研究发现嗜酸性粒细胞表达的转化生长因子(TGF- β 1)激活 SMAD 信号通路是促进膜发育的持续性纤维化的重要机制[14]。血肿包膜不断成熟导致包膜内血肿液被局限在包膜内,限制了血肿液的完整吸收。

2.3. 血肿增加机制

“出血”也是导致患者硬膜下血肿不断增大并出现临床症状的重要因素之一,血肿包膜中可以观察到新生血管形成,而这些血管经组织学证实为不成熟的高渗透性的内皮间隙连接的大毛细血管[15],不成熟的新生血管不断渗漏血液进入相对“封闭”血肿腔导致血肿增多。血肿包膜中富含成纤维细胞及胶原细胞,以及“介质”,这些介质具有促进新生血管形成的作用,这些“介质”是重要的出血源,其中血管内皮生长因子(vascular endothelial growth factor, VEGF)是最重要的促血管生成因子,参与增强微血管的通透性,有大量证据表明,与外周血和脑脊液(Cerebro-Spinal Fluid, CSF)相比,在 cSDH 液中发现 VEGF 和 VEGF-R 的浓度显著更高[16]-[18],血肿液中过高的 VEGF 可能是由新生血管内皮产生[19]。血肿包膜上形成不成熟的新生血管后,血液“渗出”到血肿腔内,当吸收的血液少于渗出的血液时,进入一种循环,慢性血肿不断形成并增加,直到患者最终出现临床表现。基质金属蛋白酶(MMPs)是一种蛋白水解酶,其会消化细胞外基质,其由血管内皮细胞释放[20]。其参与炎症反应,表现为增加血管通透性,有研究证实 MMPs 和 VEGF 共同导致新生血管不稳定使出血风险增加。cSDH 膜和液体中存在 MMP-1、-2、-9,这可能是导致脆弱、渗漏毛细血管形成的因素[18][21]。MMP-2 和 MMP-9 的水平也与 VEGF 浓度相关,表明存在联合的血管生成过程[18]。

血肿同时形成炎性细胞,如:中性粒细胞、巨噬细胞、淋巴细胞、嗜酸性粒细胞等。炎性细胞产生炎性细胞因子,炎性细胞因子为修复损伤聚集在硬膜下空间,在损伤修复中炎性细胞因子相互协作,促进组织恢复,但在慢性硬膜下血的发展过程中,这种平衡似乎被打破。白介素-6 (Interleukin-6, IL-6)、白介素-8 (Interleukin-8, IL-8)是 cSDH 中重要的炎性因子,血肿腔内液体中 IL-6、IL-8 显著升高[22]。Osuka 等[23][24]在 cSDH 外膜的成纤维细胞中发现 Janus 激酶信号转导子和转录激活子(JAKSTAT)信号通路的激活,并受多种细胞因子(包括高浓度 IL-6)的调节。在成纤维细胞和内皮细胞中观察到特别显著水平的活化的 STAT3,这可能提示 IL-6 对 cSDH 包膜生长起潜在的促进作用。IL-8 在血管生成中起重要作用,其导致毛细血管形成、内皮细胞增殖和 MMP-2 释放[25]。更有意义的是目前多项研究发现,炎性因子与 cSDH 复发风险增加相关[26]。值得一提的是有部分 cSDH 形成是从硬膜下积液转化而来,其开始并无外伤及出血,有研究认为其转化为血肿可能是因为积液引发了炎症反应从而导致新生血管的形成并出血,这与外伤导致的 cSDH 机制是相似的[27]。

当新鲜的血凝块集中在硬膜下时,纤溶系统被激活,其中的凝血酶将纤维蛋白原裂解为纤维蛋白,纤维蛋白在纤溶酶的作用下被分解为纤维蛋白降解产物(Fibrin Degradation Products, FDP)并促进包膜内血凝块的分解。纤溶酶的形成主要依赖于纤溶酶原激活剂(tissue plasminogen activator, t-PA),并且血肿包

膜上血管可释放 t-PA 至血肿腔。Hiroyuki 等[28]发现初次手术时采样 t-PA 浓度较高的 cSDHs 患者复发的概率相对较高。另有研究发现, cSDH 患者血肿腔内 FDP 明显升高, 似乎证明了血肿腔内纤维蛋白过度溶解, 是导致血肿腔内不断出血的一种原因[29]。

3. 慢性硬膜下血肿术后复发机制

目前 cSDH 的一线手术治疗方案为钻孔引流术, 当患者行手术治疗后, 约 30% 的患者会出现血肿复发。寻找复发机制及降低复发率成为目前研究热点。目前血肿复发的因素有患者的共病因素、影像学上的血肿分型、解剖异常、炎症因子的相互作用等。Hyun-Jong 等[15]人测量 66 名患者血肿液中的 VEGF、IL-6 的浓度, 发现复发组 IL-6 浓度远高于非复发组。这提示术后复发可能跟血肿腔内炎症因子持续作用相关, 具体机制还需要进一步研究。CT 扫描能够检测血肿腔分离和新膜厚度。在 CT 扫描中, 新生膜厚度被视为相对于正常硬膜的异常结构, 而血肿腔分离被视为两个或多个硬膜下腔。Hongbin 等研究发现新生血肿包膜的增厚以及血肿分隔的存在是 cSDH 复发的独立危险因素[30]。新生血肿包膜增厚, 钻孔引流术无法将其清除, 而包膜促进血肿形成的病理生理机制仍存在, 导致术后复发。Liu 等[31]的一项纳入了 328 名 cSDH 患者的单中心研究发现术后血肿新生内膜的增厚可能是血肿复发的主要原因。这可能是由于传统钻孔手术虽然暂时清除了血肿并缓解了血肿的占位效应, 但血肿包膜仍然存在, 包膜减缓了患者脑复张速度, 同时硬脑膜修复时新血管形成时微血管渗血导致硬膜下血肿增加复发。

4. 慢性硬膜下血肿术后复发的预防

脑膜中动脉栓塞术(middle meningeal artery embolization, MMAE)是一种减少 cSDH 血肿血液供应的血管内治疗方式, Mandai 等[32]在 2000 年的一份病例报告中首次探讨了 MMAE。研究发现脑膜中动脉是多数 cSDH 的供血动脉[33], 栓塞脑膜中动脉可以切断血肿的血液供应, 从而降低 cSDH 的复发率。Akira 等[34]将 MMAE 作为治疗复发型 cSDH 的手术方式, 其筛选出 5 例手术后反复复发的患者接受 MMAE, 5 位在接受栓塞术后均未再复发。Eimad 等[35]将具有独立复发危险因素的 89 例患者进行联合手术与 174 例只进行排空手术患者进行对照, 联合手术组有 4 例(4%) cSDH 复发需要手术治疗, 显著低于对照组的 24 例(14%)。Davies 等[36]的一项前瞻性研究纳入了 400 例有伴随症状的 cSDH 患者, 研究发现 MMAE 手术组复发及血肿进展率小于对照组。这是目前现有研究中样本量较大的前瞻性研究, 其证实了 MMAE 的安全性及疗效, 对于降低复发率的结果令人鼓舞。cSDH 中还有一种较为特殊的类型, 分隔型 cSDH, 这种类型 cSDH 以血肿间形成间隔, 且传统手术不易彻底清除血肿, 其本身也是 cSDH 复发的影响因素。Martinez-Gutierrez 等[37]的一项纳入 80 例 cSDH 病例的研究中 63.8% 的患者接受了 MMAE 联合手术治疗, 研究将其分为分隔组与无分隔组, 分隔组复发率较低(3.1%), 且术后血肿厚度减少更多。一定程度上体现出 MMAE 联合钻孔引流术可以进一步降低分隔型 cSDH 术后复发率。目前可以通过术前的影像学评估患者血肿包膜、新生血管、分隔等情况后识别高危复发人群后针对高危复发人群行 MMAE 降低患者术后复发率。今后可能需要逐步建立系统评估表对 cSDH 患者进行评估决定个体化手术方案进一步降低 cSDH 复发率。

5. 讨论

慢性硬膜下血肿因其发病率上升、临床症状多变、一线手术治疗复发率高等特点使其在近几年成为研究热点。随着其病理、生理机制的不断明确, 新型血管内治疗方式脑膜中动脉栓塞术被证实可以从病理生理机制的角度防止 cSDH 复发。阿托伐他汀也被证实有促进幼稚血管成熟的作用, 可以有效治疗无症状 cSDH。这些治疗中的进展均是因为病理生理机制的明确。但血肿发生机制中还有一部分并未完全明

确, 比如部分硬膜下积液发展为慢性硬膜下血肿的机制。目前现有研究中关于血肿发生和复发病理生理机制多通过临床中收集血肿液或血肿包膜进行实验室或病理检查进行研究, 可能还有一些更深层的机制通路有待研究。相信未来通过更多的基础、临床研究不断明确 cSDH 形成及复发机制可以有效降低患者术后复发率, 使患者可以得到更加微创、有效的治疗。

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