·专题综述·

颅脑创伤脑脊液标志物研究进展

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【摘要】 颅脑创伤病理生理学机制复杂，脑脊液标志物表达变化可反映脑组织微环境改变且不易受其他因素的干扰，较血清学指标的稳定性和可靠性更高。本文综述颅脑创伤主要脑脊液标志物研究进展，以提高临床对颅脑创伤发病机制的认知，实现颅脑创伤的精准治疗。

【关键词】 脑损伤，创伤性； 生物标记； 综述

Research progress on cerebrospinal fluid markers in traumatic brain injury

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【Abstract】 The pathophysiological mechanism of traumatic brain injury (TBI) is complex, and the changes of cerebrospinal fluid markers can reflect the changes of brain microenvironment and neurometabolic processes, and are not easily interfered by peripheral factors. Compared with blood markers, they are more stable and reliable. This article reviews the research progress of main cerebrospinal fluid markers in TBI, in order to improve the understanding of the pathogenesis of TBI and achieve precise treatment of TBI.

【Key words】 Brain injuries, traumatic; Biomarkers; Review

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颅脑创伤(TBI)病理生理学机制复杂且临床表现具有异质性，诊断主要依靠神经影像学及神经系统体格检查，缺乏实验室指标，积极探究高敏感性和特异性的体液标志物对颅脑创伤的精准诊断、疾病分级和预后预测具有重要意义。颅脑创伤血清学标志物特异性较低，易受其他因素的干扰；脑脊液标志物则可反映脑组织微环境改变，较血清学指标稳定性和可靠性更高[1]。近年研究相继发现，神经元特异性烯醇化酶(NSE)、S-100B蛋白(S-100B)、tau蛋白、神经丝轻链(NfL)、泛素羧基末端水解酶L1(UCH-L1)等生物学标志物与颅脑创伤密切相关。新近发现的短肽和神经鞘片段、基质金属蛋白酶(MMPs)、嘌呤、细胞外囊泡(EVs)和外泌体等在预测颅脑创伤预后方面同样具有一定的应用前景[2]。本文拟综述上述颅脑创伤脑脊液标志物研究进展，以期提高临床对颅脑创伤发病机制的认知，实现颅脑创伤的精准治疗。

一、颅脑创伤病理生理学机制

颅脑创伤可直接引起神经元、神经胶质细胞、神经轴索、血管内皮细胞和细胞外基质等机械性损伤，损伤进一步引发继发性级联反应，包括细胞膜钠-钾ATP酶活性降低、内质网钙离子超载、线粒体损伤、氧化应激反应、神经递质失衡和血脑屏障破坏等，诱发神经-血管失耦联、代谢紊乱、胶质淋巴循环障碍、免疫炎症反应等，最终引起脑水肿、凝血功能障碍、认知功能障碍等[3-4]。因此亟待可有效反映颅脑创伤发病机制、评价创伤严重程度和预测预后的脑脊液标志物。

二、颅脑创伤脑脊液标志物

1. 神经元特异性烯醇化酶 NSE是一种急性神

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经元损伤释放的糖酵解酶，特异性表达于神经元、红细胞和神经内分泌细胞。颅脑创伤患者神经元胞膜损伤，释放的NSE进入细胞外间隙，随后进入脑脊液，透过受损的血脑屏障或胶质淋巴循环进入外周血[5]，可间接反映急性颅脑创伤严重程度，在头部CT检查未见异常的轻型颅脑创伤患者中具有较高的敏感性[6]。然而，溶血反应后红细胞胞膜上的NSE亦大量释放入血，故血清NSE特异性较差[7]。研究发现，脑脊液NSE水平与颅脑创伤严重程度以及中型和重型颅脑创伤病死率呈正相关[8]。动态监测重型颅脑创伤患者脑脊液标志物发现，NSE水平越高、病情越严重、预后越差，且NSE水平不受颅内压升高的影响[9]；重型颅脑创伤患者脑脊液NSE水平越高，神经退行性变风险越高[10]。

2. S-100B蛋白　S-100B是一种主要表达于星形胶质细胞和少突胶质细胞，并参与细胞内钙稳态调节的钙结合蛋白家族成员[11]。S-100B可反映神经胶质细胞损伤程度，中枢神经系统受损时活化的星形胶质细胞过表达S-100B并释放至细胞外间隙，脑脊液S-100B水平与颅脑创伤严重程度呈正相关关系[12]。2013年发布的《斯堪的纳维亚成人轻型颅脑创伤治疗指南》[13]推荐，轻型颅脑创伤后6小时内血清S-100B水平＜0.10 μg/L，则无需行头部CT检查和神经外科干预。然而，脂肪细胞、施万细胞和骨骼肌纤维等亦可表达S-100B，故该项指标的特异性较差。此外，S-100B的半衰期较短，易受剧烈运动、体力消耗等因素影响，导致其临床应用受到一定限制[14]。近年来有研究显示，脑脊液S-100B表达变化较少受到外界因素的影响，颅脑创伤患者脑脊液和神经细胞外液中高表达的S-100B可随时间的推移逐渐降低[15]。值得注意的是，颅脑创伤患者脑脊液和神经细胞外液除包含S-100B外，还包含其多聚体形式，因此推测S-100B可能通过与晚期糖基化终末产物受体（RAGE）和Toll样受体4（TLR4）结合，激活炎症反应，最终导致中枢神经系统损伤[15]。Shultz等[16]对16例颅脑创伤患者计91份脑脊液标本进行蛋白质组学分析，共发现1083种差异蛋白，其中还包括S-100A8、S-100A9、S-100A12，表明除S-100B外，S-100蛋白家族其他成员同样参与颅脑创伤后免疫炎症反应。

3. tau蛋白　tau蛋白参与神经轴索内细胞微管强度的调节，可反映轴突损伤程度。生理状态下，tau蛋白经磷酸化反应调节微管组装并增强微管黏弹性；颅脑创伤产生的巨大机械应力使tau蛋白过磷酸化，使蛋白异常折叠和聚集，导致血清和脑脊液tau蛋白水平异常升高[17]。研究显示，颅脑创伤后2天血清tau蛋白达峰值[18]，健康人群运动或体力消耗时血清tau蛋白水平亦升高，故血清tau蛋白的特异性较差[19]。美国匹兹堡大学和贝勒医学院联合进行的队列研究显示，中型和重型颅脑创伤患者伤后4天磷酸化tau蛋白/总tau蛋白比值升高，伤后5天脑脊液磷酸化tau181蛋白和总tau蛋白水平升高，且伤后6天内脑脊液总tau蛋白、磷酸化tau蛋白/总tau蛋白比值升高与6个月时高病残率和预后不良相关[20]。另有研究发现，颅脑创伤患者脑脊液顺式磷酸化tau231蛋白具有较高的敏感性和特异性，其在中型、重型与特重型颅脑创伤患者之间具有明显差异，可用于疾病分级，且与Glasgow昏迷量表（GCS）评分呈正相关关系[21]。脑脊液tau蛋白水平升高与颅脑创伤后tau蛋白沉积、认知功能减退及阿尔茨海默病高发病风险密切相关[22]。美国国防部阿尔茨海默病神经影像学计划（DOD-ADNI）针对越战时期退伍军人的长期纵向研究显示，与无颅脑创伤史者相比，具有颅脑创伤史的退伍军人脑脊液总tau蛋白和磷酸化tau蛋白水平明显升高，且认知功能障碍发生率显著增加[23]。

4. 神经丝蛋白　神经丝蛋白（NFP）由神经丝轻链、神经丝中链（NfM）和神经丝重链（NfH）共3种不同的多肽亚基组成，参与调节细胞骨架完整性，可反映神经元和神经轴突损伤[24]。磷酸化神经丝蛋白具有生物活性，可促进神经元和神经轴突稳定性。颅脑创伤后神经元凋亡，神经轴突解体，细胞骨架蛋白水解，神经丝蛋白去磷酸化并释放至脑脊液和血液[24]，其中神经丝轻链是最具前景的生物学标志物[25]。一项基于职业冰球运动员脑震荡症状的前瞻性研究显示，脑脊液和血清神经丝轻链表达变化趋势较一致，且二者与脑震荡次数和严重程度呈正相关关系[26]。此外，脑脊液神经丝轻链水平与灰质和白质体积呈负相关，与白质完整性呈正相关关系[25]；磷酸化神经丝轻链同样是神经轴突损伤的特异性生物学标志物，尤其是白质轴突[27]。

5. 泛素羧基末端水解酶L1　UCH-L1是一种表达于神经细胞胞质的重要蛋白，通过泛素化作用清除体内过量蛋白，其水平可以反映神经细胞的损伤程度。颅脑创伤后神经细胞损伤，胞质内UCH-L1释放至细胞外间隙，并随血脑屏障的破坏进入外周

血[28]。研究显示,颅脑创伤后6小时血清和脑脊液UCH-L1水平升高,至伤后8小时达峰值,其半衰期为12小时[29]。UCH-L1亦可以用于评价颅脑创伤严重程度和预测预后,研究显示,头部CT阴性与阳性患者UCH-L1水平存在显著差异,进而为未合并颅内出血的颅脑创伤患者提供精准诊断,避免非必要的CT检查[30];重型颅脑创伤患者伤后6小时血清和脑脊液UCH-L1水平升高与伤后3个月内病死率密切相关[31]。

6.短肽和神经鞘片段 Brevican和Neucan是中枢神经系统细胞外基质中的特异性蛋白多糖,参与调节轴突形成和突触连接,前者属于短肽,后者属于神经鞘[32]。颅脑创伤后细胞外基质中Brevican和Neucan在损伤部位释放,随后被具有血小板反应蛋白活性的整合素样金属蛋白酶与凝血酶(ADAMTS)水解并释放进入脑脊液[33]。研究显示,与特发性正常压力脑积水患者相比,颅脑创伤患者ADAMTS活性更强,脑脊液短肽和神经鞘水平更低,其中短肽B741和B834表达水平与预后不良呈负相关关系,有望成为预测颅脑创伤预后的生物学标志物[34]。

7.金属基质蛋白酶 MMPs是一种参与细胞外基质蛋白降解的蛋白家族,颅脑创伤后MMPs水平显著升高,可引起继发性脑损伤和血脑屏障破坏,有望成为预测颅脑创伤预后的生物学标志物[35]。Minta等[36]对比分析33例颅脑创伤患者与38例特发性正常压力脑积水患者脑脊液MMPs表达变化,发现二者MMP-2、MMP-9和MMP-12水平无明显差异,而颅脑创伤患者MMP-1、MMP-3和MMP-10水平高于特发性正常压力脑积水患者并随时间的推移逐渐降低,其中脑脊液MMP-10水平升高与预后不良密切相关,有望成为预测颅脑创伤预后的生物学标志物。

8.嘌呤 中枢神经系统中嘌呤物质作为神经递质不仅在维持神经细胞功能和神经系统内环境稳态中发挥重要作用,而且可调节突触传递和各种高级神经功能[37]。最新研究发现,重型颅脑创伤患者脑脊液鸟苷二磷酸、鸟苷、腺苷、肌苷、次黄嘌呤和黄嘌呤水平显著升高,且入院后2~4小时脑脊液GTP水平与病死率呈正相关关系,出院2年后脑脊液鸟苷水平与改良Rankin量表(mRS)评分呈负相关关系,提示脑脊液嘌呤水平对预测颅脑创伤预后具有一定价值[38]。

9.细胞外囊泡和外泌体 细胞外囊泡和外泌体是由多种细胞如神经胶质细胞、神经元、血管内皮细胞、白细胞分泌并参与细胞间信号转导的囊泡和膜性颗粒,囊泡内携带多种蛋白及核酸物质[39]。研究发现,重型颅脑创伤后脑脊液细胞外囊泡和(或)外泌体水平显著升高,可诱发创伤性凝血病、炎症反应、血脑屏障破坏、脑水肿、神经退行性变等病理过程[40]。蛋白质组学分析显示,颅脑创伤后脑脊液细胞外囊泡和(或)外泌体中存在多种蛋白,如细胞骨架蛋白、轴突生长相关蛋白、细胞外基质蛋白和细胞信号调节因子等,不仅参与调控细胞死亡和神经退行性变相关信号转导[41],而且可间接反映颅脑创伤复杂的病理生理学机制,二者有望成为具有应用前景的颅脑创伤生物学标志物。

10.其他 颅脑创伤患者脑脊液多种可溶性蛋白如白细胞介素(IL)、CC趋化因子配体2(CCL2)、肿瘤坏死因子-α(TNF-α)等呈现一系列变化,可反映其复杂的免疫炎症过程[42];此外,不同严重程度和预后颅脑创伤患者脑脊液微小RNA(miRNA)如miRNA-320c、miRNA-92a和miRNA-30水平在疾病不同阶段存在显著差异,可评价创伤严重程度和预测预后,具有良好的应用前景[43]。未来尚待不断筛选出敏感性和特异性更高的标志物,以指导颅脑创伤的分子诊断与精准治疗。

综上所述,颅脑创伤的病理生理学机制复杂,不仅涉及细胞水平如神经细胞、神经轴突和血管内皮等损伤,同时还涉及亚细胞水平如线粒体损伤、氧化应激反应、细胞外囊泡和外泌体释放等。生物学标志物可间接反映上述病理生理学过程,密切监测颅脑创伤患者脑脊液标志物可在一定程度上避免轻型患者非必要的影像学检查和神经外科干预,同时对于中型和重型患者具有一定预后预测价值,甚至可为颅脑创伤提供新的治疗靶点。

利益冲突 无

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·小词典·

中英文对照名词词汇（三）

颅脑创伤 traumatic brain injury（TBI）
颅咽管瘤 craniopharyngioma（CP）
美国创伤外科协会
American Association for the Surgery of Trauma（AAST）
美国国防部阿尔茨海默病神经影像学计划
Department of Defense Alzheimer's Disease Neuroimaging Initiative（DOD-ADNI）
美国心脏协会 American Heart Association（AHA）
美国胸科医师学会
American College of Chest Physicians（ACCP）
美国卒中协会 American Stroke Association（ASA）
弥散性血管内凝血
disseminated intravascular coagulation（DIC）
免疫抵抗型 immune resistance（IR）
免疫检查点阻断 immune checkpoint blockade（ICB）
面-臂肌张力障碍发作
faciobrachial dystonic seizures（FBDS）
模式识别受体 pattern recognition receptor（PRR）
囊泡相关膜蛋白8
vesicle-associated membrane protein 8（VAMP8）
脑干听觉诱发电位
brain stem auditory-evoked potential（BAEP）
鸟苷二磷酸 guanosine diphosphate（GDP）
凝血酶原活动度 prothrombin time activity（PTA）
凝血酶原时间 prothrombin time（PT）
胚胎干细胞 embryonic stem cells（ESCs）
普通肝素 unfractioned heparin（UFH）
CC趋化因子配体2 chemokine (C-C motif) ligand 2（CCL2）
CX3C趋化因子受体1
chemokine (C-X3-C motif) recepter 1（CX3CR1）
全面无反应性量表
Full Outline of Unresponsiveness Scale（FOUR）
全面性强直-阵挛发作
generalized tonic-clonic seizure（GTCS）
全外显子组测序 whole exome sequencing（WES）
缺氧缺血性脑病 hypoxic-ischemic encephalopathy（HIE）
缺氧诱导因子-1α hpoxia-inducible factor-1α（HIF-1α）