

NLR与脑出血预后关系的研究进展

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【摘要】 脑出血具有病残率高和病死率高的特点。炎症反应与脑出血病程密切相关,脑出血后白细胞释放炎性介质与细胞毒性介质,通过提高毛细血管通透性、促进细胞肿胀,损伤血脑屏障,进而增强病变周围水肿,影响脑出血的临床病程。因此,炎症标志物有助于判断脑出血发展过程及预后。在炎症反应中,中性粒细胞和淋巴细胞是两类主要参与者,中性粒细胞与淋巴细胞比值(NLR)则整合了这两类细胞的信息,是炎症反应的可靠指标,该比值在临床应用中存在一定的潜在价值。本文结合相关研究,重点阐述NLR在脑出血后发展过程中的相关作用机制及对预后评估的意义。

【关键词】 脑出血; 中性粒细胞; 淋巴细胞; 炎症; 预后; 综述

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Research progress on the relationship between NLR and prognosis of intracerebral hemorrhage

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【Abstract】 Intracerebral hemorrhage is characterized by high morbidity and mortality. Inflammatory response is closely related to the course of intracerebral hemorrhage. After intracerebral hemorrhage, white blood cells release inflammatory and cytotoxic mediators, which promote capillary permeability, cell swelling and damage the blood-brain barrier, enhance edema around the lesion, and then affect the clinical course of intracerebral hemorrhage. Thus, evaluation of inflammatory markers is helpful for the development and prognosis of intracerebral hemorrhage. In the inflammatory response, neutrophils and lymphocytes are the two main players, and the neutrophil to lymphocyte ratio (NLR) integrates the information of both neutrophils and lymphocytes, is a reliable indicator of inflammatory response, and the ratio has certain potential value in clinical application. This article reviews the relevant mechanism and prognosis of NLR after intracerebral hemorrhage in combination with related research in recent years.

【Key words】 Cerebral hemorrhage; Neutrophils; Lymphocytes; Inflammation; Prognosis; Review

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脑出血的发病率在卒中各亚型中仅次于缺血性卒中,位居第二。脑出血具有发病率高、病残率高和病死率高的特点,我国脑出血占全部住院卒中的比例为18.8%~47.6%^[1]。因此,在入院时评估脑出血患者病情严重程度,并对其进行分类,依此制订合适的治疗计划,对改善患者预后、降低病死率及病残率具有重要意义。继发性脑损伤是脑出血预后不良的主要影响因素之一^[2]。颅内血肿形成后的占位效应及全身炎症反应,会导致继发性神经功能恶化,

所以炎症反应是继发性脑损伤中的重要一环^[3-5]。

中性粒细胞与淋巴细胞比值(neutrophil to lymphocyte ratio, NLR)作为一种新兴的评估疾病的炎症标志物,可以综合反映机体免疫炎症状态。多项研究表明,NLR可以清晰地预测多种重大疾病的预后,如菌血症、急性冠脉综合征、肿瘤和缺血性卒中等^[6-8]。目前,全球范围内关于NLR与脑出血预后相关性的研究日益增多。本文主要阐述NLR在脑出血后的作用机制及在预后评估中的作用。

一、预测脑出血预后的方法

早期、准确识别脑出血患者的病情严重程度并判断其预后,是医生诊治脑出血患者时面临的较为迫切的问题。既往报道中,脑出血预后不良的重要风险预测因素包括入院时格拉斯哥昏迷评分(Glasgow Coma Scale, GCS)、脑出血评分、出血的位置和体积、CT征象为混合征、中线移位、血糖和尿酸。研究证明,早期有临床意义的神经系统改变与脑出血患者的远期预后相关^[9]。入院时的GCS评分可预测脑出血患者的预后^[10-11],脑出血评分可作为脑出血患者30 d病死率的独立预测因素^[12]。虽然脑干出血量对比小脑出血往往相对较小,但与小脑出血患者的预后相比,脑干出血患者的病死率更高^[13]。两项研究表明,中线移位可用于预测脑出血患者的功能结局^[14-15]。此外有研究表明,CT征象为混合征与CT血管造影点征呈正相关,并可预测急性脑出血后继发性神经功能恶化^[16]。高血糖和炎症反应可能通过多种复杂的病理机制相互作用,促使继发性脑损伤的发生,对脑出血患者的预后产生不良影响^[17]。动物实验证明,低尿酸水平可以通过一系列生物学和生理机制引起炎症和脑血管结构退化,最终导致血管破裂和预后不良^[18]。及时并准确地预测脑出血预后具有重要意义,可以帮助临床医生判断干预措施的治疗效果,从而为患者制订更有益的治疗方案。当前评估脑出血预后的方法较多,但大多基于丰富的临床识别经验并具有一定的局限性,不能准确地预测脑出血结局。

二、炎症反应与脑出血

脑出血后的机体免疫反应可启动炎症级联反应,进而影响脑出血的临床病程。炎症反应的严重程度可以通过临床表现如发热、神经功能恶化和生化炎症标志物如中性粒细胞、淋巴细胞、CRP、TNF- α 、IL-1、IL-6和基质金属蛋白酶-9等来评估。对这些中枢炎症的外周标志物进行分析,能为潜在病理生理学提供参考,并可能为临床实践和未来的研究提供启示。因此,通过评估炎症反应的生物标志物,可以更多地了解急性脑出血损伤的过程和机制。

1. 中性粒细胞与脑出血的关系:成年人外周血中的中性粒细胞数量占白细胞总数的55%~70%,在自身免疫系统疾病、肿瘤、慢性炎症反应性疾病等疾病的发生和发展中具有重要作用,在脑出血发病过程中的作用也较为重要。脑出血后,血肿周围的小胶质细胞最先对损伤做出反应,释放多种促炎因子和趋化因子募集外周炎性细胞迁移到脑损伤区^[19]。浸润的白细胞释放炎性介质与细胞毒性介质,通过提高毛细血管通透性、促进细胞肿胀,损伤

血脑屏障,进而增强病变周围水肿^[20-21]。其中,中性粒细胞率先到达血肿周围。临床病理结果和动物实验表明,中性粒细胞在脑出血后6 h便开始渗入脑内,在1~3 d达到高峰,其在外周免疫细胞中发挥主要作用^[22]。中性粒细胞诱导的神经毒性和多种途径相关联,包括细胞毒性介质与TNF- α 、IL-1、IL-6等促炎细胞因子的分泌、基质金属蛋白酶-9的上调、巨噬细胞的活化以及活性氧的过度产生^[23]。这导致了毛细血管通透性增高、血脑屏障破坏和细胞肿胀,进一步促使血肿生长和水肿形成,引起颅内压增高,造成脑组织移位,从而对卒中恢复产生负面影响^[24-27]。

此后,中性粒细胞水平在2~3 d后下降,有助于恢复血脑屏障完整性和改善预后。相关研究表明,早期外周血中性粒细胞增加是出血周围水肿发展的独立预测因素,是脑血肿后继发性损伤的炎性标志物,也是神经功能早期恶化和预后不良的一个危险因素^[28]。在动物模型中,如果在脑出血前选择性消耗外周血中性粒细胞,可以减少脑出血后小胶质细胞的活化以及外周血中性粒细胞和单核细胞的浸润,从而减轻炎症反应和血脑屏障的破坏程度^[29-30]。同样,脑出血后早期抑制中性粒细胞来源的基质金属蛋白酶,对早期脑出血诱发的脑损伤有保护神经的作用^[31-32],其可减少胶质细胞活化和神经细胞凋亡,减小损伤体积,改善神经恢复^[33]。综上所述,中性粒细胞在脑出血后能快速浸润受损脑组织并释放一系列溶酶体物质,而这些物质可引起周围脑组织和血管的损伤,对患者机体造成一定的伤害,进而导致继发性脑损害,从而加重脑出血患者的病情。因此,中性粒细胞水平的升高可提示继发性脑损害的发生。

2. 淋巴细胞与脑出血的关系:淋巴细胞作为机体细胞免疫和体液免疫的重要组成部分,是宿主抵御病原体过程中必不可少的免疫细胞。在中枢神经系统中,T细胞的存在通常被认为具有致病性。然而,一项研究显示,T细胞在健康人群的脑脊液中“巡逻”以维持对CNS的免疫监视,这表明T细胞存在于健康人群的CNS中,并在其中发挥功能^[34]。T细胞的两个主要亚型,CD4⁺T细胞和CD8⁺T细胞,两者协同工作介导免疫相关的细胞死亡。在还原作用下,CD4⁺T细胞还可活化其他细胞,如B细胞和巨噬细胞;CD8⁺T细胞能杀死有害或受损的细胞。在自体血脑出血模型中,过继转移调节性T细胞可通过抑制经典活化小胶质细胞的效果,缓解局部脑出血后的炎性反应,从而改善血脑屏障的稳定性,减轻脑水肿,并减少神经细胞的死亡^[35]。同样有研究表

明,脑损伤后12 h内淋巴细胞的减少是脑损伤的标志^[36],大脑和机体免疫的作用是双向的,CNS急性损伤的同时会对免疫功能造成较大的影响。

在脑出血的最初几天,CNS与下丘脑-垂体-肾上腺轴的过度激活,导致体液和激素环境改变,如儿茶酚胺和类固醇的水平急剧增加,诱导外周血淋巴细胞的凋亡和功能失活。因此,卒中后存在一定程度的免疫抑制和抗菌免疫反应受损^[37-39]。在基础实验研究中,卒中后免疫功能受到抑制可造成自发性细菌感染,引起感染并发症,如高热、酸中毒、缺氧、电解质紊乱和凝血功能异常等,这些并发症都会导致脑出血后发病率和病死率增加^[40]。此外,低淋巴细胞百分比也是脑出血患者感染发生率的独立预测因素^[38, 41-42]。淋巴细胞凋亡是免疫抑制的主要因素之一,机体通过调节淋巴细胞,进而影响脑出血的发病过程,淋巴细胞在脑出血后具有抗炎和保护血管内皮的作用,因此淋巴细胞百分比与脑出血预后密切相关。

3. NLR与脑出血的关系:目前,脑出血患者预后评估模型中的预测因素如脑出血评分、GCS评分等,主要基于患者的临床信息进行评估,主观性较强,缺乏对实验室生物标志物的判断。探索NLR对脑出血预后的价值,为脑出血预后评估指标提供了新的研究思路。脑出血急性期常需要进行动态血常规检查,便于获得NLR峰值。因此,NLR正迅速成为多种神经系统疾病,如卒中、多发性硬化和创伤性颅脑损伤的客观、易获得、低成本和可重复性的预后指标。

从临床角度看,虽然没有感染的证据,但相当比例的脑出血患者在急性期常被观察到外周血白细胞计数升高。一项研究表明,外周血中性粒细胞数量增加可能导致中枢中性粒细胞浸润,导致不良结局^[43],而中性粒细胞水平升高和淋巴细胞水平降低的患者在缺血性和出血性卒中中的转归较差^[44]。单独考虑每种炎症标志物似乎不足以充分预测结局,但将它们与NLR结合,预测价值提高。已有研究表明,作为神经系统恶化的预测指标,NLR优于白细胞计数,且NLR是一个更可靠的功能结局预测因子^[45]。脑出血后,NLR可能反映了急性脑出血患者局部和全身的炎症反应水平^[46]。Chen等^[47]推测,在脑出血的发生和发展过程中,炎症反应逐渐增强,NLR相应升高,随着病情好转,炎症反应逐渐消退,NLR相应降低。一项研究强调,在评估脑出血预后的简单且经济的指标中,NLR似乎是最佳的炎症相关标志物^[48-49]。作为炎症检查的实验室指标,NLR不受运动和脱水

的影响^[50]。多项研究表明,脑出血后存活的患者入院后1周内NLR水平相对稳定,与之对应的30 d内死亡患者的早期NLR则上升,因此可以监测这段时间内脑出血患者NLR的动态变化^[51-53]。而入院后72 h NLR也已被确定为脑出血患者病死率和不良结局的独立预测因素^[44, 54]。健康成人的NLR正常值为0.78~3.53^[55]。NLR轻度升高可能在脑出血患者1年的功能预后方面发挥保护作用,这可能与中性粒细胞固有的促进神经保护和吞噬修复的功能有关,而相对稳定的淋巴细胞数量也在一定程度上预防了感染并发症的发生^[46]。当脑出血发病1周内NLR>5~7时,NLR的升高与不良预后相关^[56],且早期NLR值的升高可以预测血性水肿的增长^[28]、发生感染的风险、早期神经功能恶化的发生^[57]以及短期院内病死率的上升^[51, 58]。

手术治疗可阻止血肿扩大,阻断血肿炎性产物释放,从而干预疾病发病后的病理过程。然而,上述研究并未考虑手术治疗是脑出血治疗方法的重要组成部分。有研究显示,与中性粒细胞与淋巴细胞相比,入院时NLR对脑出血手术患者的功能预后具有更好的预测能力,NLR的增加与脑出血患者血肿清除术后30 d病死率和90 d不良转归独立相关^[59-60]。术后48 h内的NLR比其他时间点的NLR对脑出血手术患者的预后具有更大的预测价值,对于接受微创穿刺引流术或开颅手术患者而言,术后48 h内的NLR预测不良预后的峰值分别为12.35和14.46^[61]。

NLR作为一种炎症指标,使用简单,无需依赖丰富的临床识别经验。因此,在治疗过程中可更加关注NLR,尤其是NLR峰值,该值需在入院诊断的辅助实验室检查的基础上完成,并可在脑出血急性期进行评估。

三、总结与展望

NLR对于脑出血的病情严重程度以及预后评估具有重要意义,同时由于脑出血的病程进展是一个动态的过程,在整个发病过程中NLR值也会不断发生变化,因此动态监测NLR的变化对于脑出血患者的病情和预后评估可能更有意义。作为炎症指标,NLR能够反映出患者的免疫状态,并且在常规检查中易于获得,结果较为客观、标准,并且具有创伤小、可重复性高、价格便宜等优点。因此,NLR具有普及的临床应用意义。

但不足之处是,脑出血预后相关影响因素较多,只做NLR与脑出血预后分析存在一定的局限性,需同时结合患者临床表现与影像学表现对预后进行评

估。目前NLR尚无准确的分界值,未来需要更多大样本、多中心的高质量研究来证实NLR对于脑出血患者预后的指导价值。病例对照研究也有助于明确其正常范围,并可根据年龄类别进行调整。炎症反应在脑出血发病期间扮演着重要角色,目前应用抗炎药物减轻全身炎症反应来改善脑出血患者不良预后和短期病死率的研究仍较少,因此将抗炎药物用于脑出血治疗以延缓疾病的进程,减少并发症的发生,可能成为今后研究的热点。

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外泌体在心境障碍中诊断及治疗的研究进展

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【摘要】 外泌体作为一种纳米级别的细胞外囊泡, 内含多种生物活性物质, 其广泛参与细胞间物质运输与信息传递, 并在多种病理生理过程中发挥重要作用。心境障碍常因其临床复杂性而导致识别困难、诊断不明确以及治疗难度大。心境障碍患者的外泌体在数量及表型上与健康对照者相比存在差异。现对心境障碍患者外泌体的相关研究进行综述, 探讨不同来源的外泌体作为心境障碍生物诊断标志物以及治疗靶点的可能性。

【关键词】 抑郁症; 双相情感障碍; 心境障碍; 外泌体; 生物标志物; 综述

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【Abstract】 Exosomes are nanoscale extracellular vesicles containing a variety of bioactive substances that are widely involved in intercellular material transport and information transfer, and play an important role in a variety of pathophysiological processes. Mood disorders often result in difficulty in recognition, unclear diagnosis, and difficult treatment due to their clinical complexity. There are differences in the quantity and phenotype of exosomes between patients with mood disorders and healthy controls. This article reviews the relevant research on exosomes in patients with mood disorders, and explores the possibility of exosomes from different sources as biological diagnostic markers as well as therapeutic targets for mood disorders.

【Key words】 Major depressive disorder; Bipolar disorder; Mood disorder; Exosome; Biomarker; Review

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