·神经系统疾病免疫研究进展·

衰弱与炎症

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【摘要】 衰弱作为一种老年综合征，使老年人不良健康结果如跌倒、抑郁、残疾、失能和死亡等增加，其发病机制尚未明确，慢性炎症被认为是其发生发展的主要机制。炎症反应通过导致肌少症、肥胖、多种慢性病以及免疫功能下降等病理生理学机制而诱发衰弱。营养支持、药物治疗和运动干预等措施可降低炎性因子水平，减轻炎症反应，从而促进肌肉生长、减少肥胖，对衰弱有一定改善作用。

【关键词】 炎症； 蛋白质能量营养不良； 综述

Frailty and inflammation

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【Abstract】 Frailty, as a kind of geriatric syndrome, increases adverse health outcomes such as falls, depression, deformity, disability and death in the elderly. The pathogenesis of frailty is not yet clear, and chronic inflammation is considered to be the main mechanism for its occurrence and development. Inflammation induces frailty by leading to sarcopenia, obesity, a variety of chronic diseases and immune dysfunction. Nutrition support, drug therapy and exercise intervention can reduce the level of inflammatory factors, reduce the inflammatory response, thus promoting muscle growth, reduce obesity, have a certain improvement effect on frailty.

【Key words】 Inflammation; Protein-energy malnutrition; Review

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衰弱是一种临床常见的老年综合征，主要表现为生理储备减少、脆弱度增加，可导致严重的不良后果，如跌倒、抑郁、残疾、失能、死亡等[1]。衰弱是一种非特异性状态，涉及多器官系统的病理生理变化，据心血管健康研究（CHS）估计，衰弱正在成为影响老年人的最重要的临床症状之一[2]。

目前，衰弱的发病机制尚未阐明，慢性炎症反应被认为是其关键发病机制[3]。炎性因子通过不同的病理生理通路直接或间接导致衰弱的发生。长期慢性低水平炎症可使靶器官处于过度反应状态，机体内炎性因子如白细胞介素（IL）、肿瘤坏死因子（TNF）、C-反应蛋白（CRP）和白细胞计数升高，通过氧化应激、细胞周期阻滞、细胞凋亡等途径诱导局部组织和多器官系统损伤，从而导致衰弱。研究显示，慢性炎症是老年相关疾病的重要原因之一，可以导致衰弱[4]，本文拟就炎症与衰弱之间的关系进行综述。

一、炎症导致衰弱的原因

1. 衰弱与肌少症 肌少症（sarcopenia）是一种肌肉质量、力量和功能下降性综合征，在老年人群中较为常见，被认为是衰弱的主要物理驱动因素之一，甚至可能是衰弱的前兆状态。慢性炎症被认为是导致肌少症和衰弱的原因。研究显示，肌少症与

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血浆TNF-α和IL-6水平升高具有相关性[5]；血清高IL-6不仅可以预测肌少症的发生[6]，同时还可预测肌少症和衰弱的结果，如失能、死亡等[7]；此外，血清IL-6、CRP水平升高与握力降低亦具有关联性[8]，基线评价时高IL-6和CRP提示3年内握力降低＞40%的风险增加2～3倍[6]。随着年龄的增长，血清炎性因子如IL-6和1β、CRP、TNF-α水平显著升高，与肌肉质量、力量和功能减退呈正相关[9]，CRP水平升高还与蛋白质合成减少和分解代谢增加有关[10]；此外，上述炎性因子还可通过间接降低机体生长激素（GH）和胰岛素样生长因子-1（IGF-1）水平，而减少蛋白质的合成，导致肌少症[11]。与非肌少症患者相比，肌少症患者外周血白细胞计数和中性粒细胞计数增加[12]，其中，中性粒细胞计数增加与低体力活动和衰弱相关[13]。中性粒细胞的趋化能力可随着年龄的增长而显著降低，当趋化能力低下的中性粒细胞发生迁移时，可产生更多的组织损伤并继发全身性炎症反应[14]，因此，中性粒细胞的异常迁移可对肌肉造成继发性损伤，导致肌细胞损伤、凋亡以及肌纤维丢失，这种肌肉数量和质量的丧失可导致功能丧失和衰弱。

2. 衰弱与肥胖　脂肪组织具有活跃的内分泌功能，其分泌的细胞因子可影响全身炎症反应状态。脂肪组织中的脂肪细胞和浸润的巨噬细胞可产生脂肪因子和炎性因子，如TNF-α、IL-6和瘦素（leptin），这些因子可诱导肝细胞产生CRP，而炎性因子分泌增多则可使骨骼肌分解代谢加快。研究显示，肥胖个体的骨骼和肌肉质量较低，而血清CRP水平较高[15]。衰弱患者体重指数（BMI）较衰弱前期和健康人群明显增加[16]；同时，肌少症可以导致体力活动减少，使肥胖风险增加，而脂肪含量的增加可以通过慢性炎症反应再次介导肌少症的发生[17]。随着年龄的增长，机体组成成分不断变化，如骨密度降低、肌肉减少和脂肪增多，即骨骼肌减少性肥胖（SOB）[18-19]，主要表现为脂肪细胞在肌肉中异位沉积导致骨骼肌减少和萎缩，与老年人残疾、失能等常见并发症有关[20-21]。

3. 衰弱与慢性病　老年人常合并多种慢性病，是导致衰弱的重要危险因素之一。炎症反应与多种慢性病有关，如冠心病、慢性阻塞性肺病（COPD）、脑卒中、糖尿病、慢性肾病、恶性肿瘤和关节炎等。研究显示，炎症对老年人慢性病的发展和不利健康结果有显著促进作用[22]。老年慢性阻塞性肺病患者多合并炎症，氧化应激增强，加快细胞凋亡，使肌肉修复不良，尤其在慢性阻塞性肺病急性期更为显著，合并酸中毒时，肌肉蛋白稳定性破坏，使肌肉蛋白减少。慢性炎症亦是心血管病的重要危险因素之一[23]。2型糖尿病被认为是一种炎症反应状态，可以导致肌肉减少，促进衰弱的发生。慢性炎症可增加恶性肿瘤的风险，也可以促进肿瘤的进展和转移[24]。由IL-6、CRP、IGF-1等介导的慢性炎症反应是骨质疏松和衰弱共同的病理生理途径[25]。TNF-α水平与认知功能呈负相关[26]。营养摄入不足与衰弱密切相关，衰弱前期和衰弱期老年人营养状况较健康老年人差[26]。TNF-α、IL-6和CRP等炎性因子可直接或间接影响老年人的运动功能、内分泌功能、循环功能和神经功能，继而导致慢性病，并进一步参与老年人衰弱的发生、进展和转归，从而改变老年人对各种应激事件的耐受性。

4. 衰弱与免疫功能　先天性和适应性免疫功能失调可导致慢性炎症，并增加脆弱老年人对感染的易感性和严重性。外周血白细胞及其亚群是免疫系统的主要细胞成分；衰弱与白细胞计数及其各分类如中性粒细胞、单核细胞和特异性T淋巴细胞之间具有相关性，老年衰弱患者外周血中性粒细胞和单核细胞计数增加，CRP水平升高[27]。研究显示，$CD27^{-}IgD^{-}$B细胞亚群在90岁以上的老年人群中表现出较强的促炎症作用，与机体功能减退有关[28]。衰弱相关脂多糖可刺激外周血单核细胞产生IL-6，纯化的外周血单核细胞还可上调炎症反应信号转导通路中特异性基因表达，此外，单核细胞表达的CXC型趋化因子配体10（CXCL10）与衰弱相关IL-6水平升高相关[29]。上述研究表明，由免疫系统中单核细胞表达的特异性炎症反应可能导致老年人衰弱的发生。

二、衰弱及相关炎性因子的干预措施

1. 营养干预　研究显示，经过为期13周的维生素D和富含亮氨酸的乳清蛋白的营养干预，可以减轻老年肌少症患者慢性炎症反应[30]。血清维生素D水平与IL-6和CRP水平呈负相关，通过调节免疫细胞发挥抗炎症反应作用[31]。维生素D具有下调树突状细胞（DC）炎性因子表达的作用，同时可上调抗炎性因子（如IL-10）和炎症抑制分子[如免疫球蛋白样转录物3（ILT3）]的表达[32]。膳食蛋白对肌肉合成和代谢至关重要，可在对抗肌少症和慢性炎症反应中发挥重要作用。亮氨酸等氨基酸具有较强

的合成代谢作用，通过上调哺乳动物雷帕霉素靶蛋白（mTOR）信号转导通路而刺激肌肉蛋白合成、减少肌肉蛋白分解，具有抗炎症反应作用[33]。膳食中锌摄入量和血清锌水平与炎性因子IL-6、TNF-α和CRP水平呈负相关[34]，补充锌剂后IL-6水平显著下降。由此可见，对衰弱患者进行适当的营养干预可以减少炎症反应的发生。

2. 药物干预　尽管目前尚无推荐的衰弱相关药物治疗方法，但在此领域有较大的药物研发潜力。有些药物可以通过抑制慢性炎症反应，减少肌少症、慢性病的发生，从而降低衰弱的患病率。二甲双胍可降低血清CRP水平，减少全身炎症反应[35]，降低全因病死率和衰弱患病率；瑞舒伐他汀可降低血清超敏C-反应蛋白（hs-CRP）水平，从而减少血管性疾病的发病率和病死率[36]；血管紧张素转换酶抑制剂（ACEI）可通过抑制慢性炎症反应，改善肌肉功能并延缓肌少症的发生[37]。动物实验显示，卡托普利可以降低老年雌鼠血清炎性因子IL-1α、单核细胞趋化蛋白-1（MCP-1）和巨噬细胞炎性蛋白-1α（MIP-1α）水平，并升高抗炎性因子IL-10水平，减轻炎症反应，改善衰弱[38]。

3. 运动干预　衰弱包括日常生活活动能力、运动耐受力和肌肉质量下降，其中，运动耐受力降低与有氧耐力有关，阻力训练是增强肌肉力量和质量的最佳方法，因此，有规律的体育锻炼可以降低残疾风险，延缓甚至逆转衰弱。研究显示，体育锻炼具有抗炎症反应作用[39]，运动干预与血清IL-6和CRP水平呈负相关[40]。与仅接受健康教育的老年人相比，经过12个月中等强度体育锻炼的老年人血清炎性因子水平下降[41]。

随着我国人口老龄化的加剧，老年衰弱患者越来越多，由衰弱导致的不良问题，如跌倒、失能、残疾等可严重影响其生活质量，并增加家庭、医疗和社会负担。未来需要更多的研究进一步探索衰弱的发病机制，探寻适合国人的评价方法，早期筛查、及时干预、改善预后，以提高老年人的生活质量。

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