·综述·

肌少症与认知障碍的共同生物标志物研究

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【摘 要】 肌少症及认知障碍是两大常见的老年综合征,两者互为因果,肌少症使认知障碍的患病风险增加,认知障碍也可引起肌少症,最终形成恶性循环关系。早期识别肌少症和认知障碍并对其进行干预,对改善老年患者的生活质量至关重要。而生物标志物较临床表型更早出现于机体。因此,本文从炎症、激素、营养及生长因子四个方面对肌少症和认知障碍的潜在共同生物标志物进行初步探讨,以期客观及时识别肌少症和认知障碍个体。

【关键词】 肌少症;认知障碍;生物标志物
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Research on common biomarkers of sarcopenia and cognitive impairment

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【Abstract】 Sarcopenia and cognitive impairment, two common geriatric syndromes, have mutual causality. Sarcopenia increases the risk of cognitive impairment, and cognitive impairment can also cause sarcopenia, eventually developing into a vicious cycle. Early recognition and intervention of sarcopenia and cognitive impairment are crucial to improve the quality of life of the elderly patients. Biomarkers appear earlier in the body than clinical phenotypes. Therefore, this paper preliminarily discusses the potential common biomarkers of sarcopenia and cognitive impairment from four aspects, including inflammation, hormone, nutrition and growth factors, helping objective and timely identification of individuals with sarcopenia and cognitive impairment.

【Key words】 sarcopenia; cognitive impairment; biomarker
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肌少症是一种与增龄相关、进行性及全身性的骨骼肌疾病,主要表现为骨骼肌质量、力量下降和(或)伴有相关躯体功能丧失[1]。认知障碍是一种老年人常见的神经退行性病变,其特点是涉及语言、记忆、计算、推理、社会认知和执行能力等一个或多个认知领域的功能下降[2]。肌少症与认知障碍同为老年综合征,是导致老年人身体残疾及心理障碍的两个重要原因。

近期研究表明,肌少症与认知障碍存在明显的正相关性,肌少症患者中认知障碍的患病率高达40%[5]。甚至,这种关系是双向的[6],肌少症被认为是认知障碍的危险因素,认知障碍同样可以引起肌少症,两者互为因果,最终形成难以预测的恶性循环关系。且肌少症和认知障碍的共同的危险因素可能有高龄、营养不良、激素水平改变、运动减少、炎症反应及胰岛素抵抗等。故早期识别肌少症和认知障碍并对其干预,对改善老年患者的生活质量至关重要。但是肌少症与认知障碍的早期表现不典型,在临床上容易被忽视,而生物标志物可能更早、更客观地出现在机体。因此,亟需寻找肌少症和认知障碍的有效生物标志物。本文以“sarcopenia、cognitive impairment、肌少症、认知障碍”为关键词,检索“PubMed”及“万方医学”数据库近10年的相关文献,对肌少症和认知障碍的潜在共同生物标志物做如下综述。

1 炎症相关生物标志物

炎症-衰老是一种衰老过程中出现的慢性低度

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炎症状态,也是神经和身体疾病的重要危险因素。多项研究表明,血清C反应蛋白(C-reactive protein, CRP)、白细胞介素6(interleukin-6, IL-6)、肿瘤坏死因子α(tumor necrosis factor-α, TNF-α)水平与肌少症及认知障碍呈显著正相关。Westbury等[7]研究发现,随访10年后,血清CRP水平是肌少症发生的预测因子。美国一项meta分析也表明,CRP的高水平与患痴呆的风险增加显著相关[8]。此外,中国一项前瞻性研究显示,高水平的TNF-α(>11.15 pg/ml)使肌少症的风险增加7.6倍,而强化生活方式干预可显著改善肌肉质量及降低血清TNF-α水平[9]。中国另一项研究也表明轻度认知障碍患者TNF-α水平明显高于非认知障碍患者[10]。同样,Tuttle等[11] meta分析显示,较高的IL-6水平与较低的骨骼肌力量和肌肉质量之间存在明显负相关。Kurowska等[12]也发现IL-6可作为75岁以上人群认知障碍的预测因子。这些提示炎症因子CRP、IL-6、TNF-α在肌少症和认知障碍患者中可以作为简易且有前途的评价指标。

2 激素相关生物标志物

随着年龄的增长,合成代谢激素如睾酮(testosterone, T)、胰岛素样生长因子1(insulin-like growth factor-1, IGF-1)和生长激素(growth hormone, GH)水平逐渐下降。而这些激素水平的变化与肌少症及认知障碍的关系也日益明确。

2.1 睾酮

目前,较多的文章报道了血液中睾酮水平作为肌少症与认知障碍的生物标志物的潜力。研究发现,血清睾酮水平与男性肌肉质量、肌肉力量和身体表现呈正相关性[13],并且,低血清水平的游离睾酮是女性骨骼肌丧失的重要预测因子[14]。同样,Hsu等[15]队列研究也表明,老年男性血清睾酮水平的下降与认知功能的下降明显相关。其中可能的机制为睾酮具有抗炎及调节肌肉代谢的作用,从而可以增强肌肉力量及质量,促进肌肉的损伤后修复。在中枢神经系统中,睾酮也可以促进神经保护、神经发生、神经元存活以及儿茶酚胺的合成和释放。

2.2 GH和IGF-1

GH、IGF-1可以刺激肌肉的生长与再生,还可以促进神经元细胞存活和修复、神经发生、突触发生,从而有益于防止肌肉减少及认知下降。Bian等[16]研究表明,血清GH水平与老年人肌少症呈独立负相关。并且,Xu等[17]研究发现,在阻塞型睡眠呼吸暂停患者中,认知障碍患者的血清GH水平明显低于无认知障碍患者。此外,Ferrari等[18]研究表明,肌少症患者的IGF-1显著降低,在调整混杂因素后,IGF-1仍然是肌少症和低握力的重要预测指标。同样,有前瞻性研究发现,低血清IGF-1水平与阿尔茨海默病的发病风险增加有关[19]。故GH和IGF-1或可作为监测肌少症和认知障碍的血清标志物。

3 营养相关生物标志物

营养缺乏是与年龄相关疾病的危险因素之一,肌少症和认知障碍通常被认为是与营养不良相关的独立疾病。大量文献报道了营养缺乏与肌少症和认知障碍的关系。

3.1 维生素D

研究发现,低维生素D水平可能会导致肌肉力量下降,认知能力下降,并且会增加死亡风险。Okubo等[20]研究发现,在肝硬化患者中,血清25-羟基维生素D3[25-hydroxyvitamin D3, 25(OH)D3]水平低是肌少症发病率高的独立相关因素,且25(OH)D3水平与握力及骨骼肌指数呈正相关。另一方面,Ouma等[21]研究表明,血清25(OH)D3在轻度认知障碍及阿尔茨海默病的不同分期均有所降低,并且25(OH)D3是严重痴呆的唯一显著预测因子。所以,血清25(OH)D3浓度作为肌少症和认知障碍临床监测指标意义较大。

3.2 维生素B

维生素B缺乏可以表现为明显的神经肌肉问题。维生素B水平低,特别是维生素B_6、叶酸和维生素B_{12}水平低,已被发现与认知能力下降和肌少症有关。Borg等[22]研究发现,维生素B_6摄入量明显减少与肌少症发病率增高有关。Hughes等[23]研究也表明,血清较低的维生素B_6水平与认知功能的下降速率明显相关,维生素B_6是衰老过程中认识障碍的重要预测因子。此外,叶酸和维生素B_{12}也可作为监测肌少症与认知障碍的潜在血清标志物。研究发现,叶酸和维生素B_{12}缺乏的老年人肌少症[24]及认知障碍[25]患病率更高,而口服叶酸和维生素B_{12}联合治疗轻度认知障碍老年人6个月后可显著改善认知能力[26]。所以维生素B或可成为肌少症和认知障碍发生发展过程中的重要预测指标,并且可作为有效的临床干预手段。

3.3 ω-3脂肪酸

较多的研究证实了ω-3不饱和脂肪酸(n-3 polyunsaturated fatty acids, n-3PUFAs)与肌少症及认知障碍的关系。最近的meta分析表明,血液中n-3PUFAs水平较低的患者更容易患有肌少症,而长

期补充 n-3PUFAs 可以改善肌肉质量和运动性能[27]。此外,Lukaschek 等[28]研究表明,n-3PUFAs 水平较低的老年人认知障碍风险显著增高。并且,Bo 等[29]一项临床研究表明,n-3PUFAs 可以改善轻度认知障碍患者的认知功能。这些表明 n-3PUFAs 可以作为监测肌少症和认知障碍的潜在生物标志物,并且具有一定的治疗意义。

4 生长因子相关生物标志物

生长分化因子 8(growth differentiation factor-8, GDF-8)和生长分化因子 15(growth differentiation factor-15,GDF-15)是转化生长因子 β(transforming growth factor-beta,TGF-β)超家族的成员,是骨骼肌生成的负调节剂和肌肉生长的抑制剂,并且可以介导认知障碍。研究表明,肌少症患者中 GDF-8 的基因水平过表达[30],而且,Lin 等[31]在阿尔茨海默病小鼠模型中发现,高水平的 GDF-8 表达可以引发肌肉萎缩和认知障碍。此外,Kim 等[32]研究发现,血清 GDF-15 水平与小鼠模型及人类的肌肉质量和功能呈负相关。Fuchs 等[33]研究也表明,较高的 GDF-15 水平与认知功能的下降具有显著相关性,并且 GDF-15 可以预测认知衰退。

另一种与肌少症及认知障碍相关的生物标志物是脑源性神经营养因子(brain-derived neurotrophic factor,BDNF),它是一种神经营养蛋白生长因子,可通过突触增强神经发生和神经传递,促进突触生长,改善突触可塑性。研究表明,较高的血清 BNDF 水平可以预防痴呆的发生[34],且痴呆患者的血清 BDNF 水平明显低于健康对照者[35]。此外,在骨骼肌中,BDNF 还能诱导神经肌肉连接的突触增强,参与运动神经元的调节和存活,促进成肌细胞的发育和分化。Miyazaki 等[36]研究发现,严重肌少症患者的血浆 BDNF 水平显著降低,且血浆 BDNF 浓度与肌肉力量和物理性能相关。因此,GDF-8、GDF-15、BDNF 等生长因子在作为肌少症与认知障碍的生物标志物方面具有重大价值,值得进一步研究。

综上,目前的研究已发现了不同领域如炎症、激素、营养、生长因子的标志物可作为监测肌少症和认知障碍发生发展过程中的潜在共同生物标志物,但部分研究存在缺乏多中心、大样本、大队列研究等问题。因此,未来仍需大量更深入、更高质量的研究来明确更多的共同生物标志物,为肌少症和认知障碍的早期识别和及时干预等提供新的临床思路。

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