❖综述

Research status on central mechanism of chronic fatigue syndrome based on PET

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[**Abstract**] Chronic fatigue syndrome (CFS) is closely related to central system abnormalities, often associated with central nervous system symptoms such as cognitive difficulty, anxiety, depression and changes in pain perception, without specific diagnostic method. PET may provide important references for pathogenesis of CFS central system. The current status of PET for exploring central mechanisms of CFS were reviewed.

[**Keywords**] chronic fatigue syndrome; positron-emission tomography; central nervous system

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PET 研究慢性疲劳综合征中枢机制现状

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[**摘　要**] 慢性疲劳综合征(CFS)与中枢系统功能异常密切相关，常伴认知困难、焦虑抑郁及痛觉改变等，目前尚无特异性诊断方法。PET 可为研究 CFS 中枢系统异常提供重要参考依据。本文就 PET 研究 CFS 中枢机制现状进行综述。

[**关键词**] 慢性疲劳综合征；正电子发射断层显像；中枢神经系统

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慢性疲劳综合征(chronic fatigue syndrome，CFS)　又称肌痛性脑脊髓炎(myalgic encephalomyelitis，ME)，

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表现为长期存在(6 个月以上)、可致日常生活能力受损且无法解释的重度疲劳及劳累后不适,且经休息和睡眠难以缓解,常伴认知功能障碍和直立不耐受[1]。目前 CFS 病因和发病机制尚不明确,但已知其存在中枢神经系统异常[2-4]。本文就相关 PET 研究现状进行综述。

1 脑葡萄糖代谢

^{18}F-FDG 作为葡萄糖类似物可借细胞膜上葡萄糖转运蛋白进入细胞,并因无法参与下一步生化反应而滞留其中;PET 可通过识别^{18}F-FDG 显示脑部葡萄糖代谢情况,如 TIRELLI 等[5]发现 CFS 患者右额中部皮质和脑干糖代谢显著降低。CFS 患者脑部代谢可能降低,不同功能区低代谢可能与不同临床症状相关,但脑部代谢正常不能排除 CFS。SIESSMEIER 等[6]观察 26 例 CFS,发现其中 12 例双侧扣带回及邻近内侧皮质区糖代谢降低(准分数图中超 50 个相邻像素标准分数大于 2)且 5 例伴眶额区/额底皮质糖代谢降低,另 2 例楔叶和楔前叶代谢降低;右内眶额、右内颞上回及前扣带回代谢降低与抑郁症严重程度相关,双侧内颞叶与小脑交界处葡萄糖代谢降低与焦虑相关。个案报道[7]显示 1 例 CFS 治疗前双侧杏仁核(以右侧明显)和海马体/海马旁区域及双侧基底神经节、丘脑、中脑和小脑代谢降低;1 例后部皮质区域(楔前叶、顶叶、颞叶和枕叶)、杏仁核-海马复合体和小脑存在广泛代谢降低[8]。

2 中枢神经炎症机制

神经炎症反应一直是 CFS 生物标志物和发病机制的研究焦点[9-11]。18 kDa 转位蛋白(18 kDa translocator protein, TSPO)被视为神经炎症信号,参与中枢神经系统中类固醇合成并调节神经胶质激活;利用放射性核素标记配体与 TSPO 特异性结合可检测中枢神经系统炎症[12];但存在缺乏细胞特异性、无法评估免疫反应利弊等局限性。NAKATOMI 等[13]采用第一代 TSPO 示踪剂^{11}C-(R)-PK11195 行 PET 对比观察 9 例 CFS 患者[病程(5.2±7.3)年]及与之年龄和性别相匹配的 10 名健康成人,发现前者扣带回、海马、丘脑、中脑和脑桥^{11}C-(R)-PK11195 非可置换结合力(nondisplaceable binding potential, BPND)高于后者;CFS 患者^{11}C-(R)-PK11195 BPND 峰值位于左丘脑髓板内核和中脑,提示 CFS 患者存在中枢神经炎症[14-18]。而 RAIJMAKERS 等[19]对 9 例 CFS、10 例 Q 热疲劳综合征及 9 名健康人行^{11}C-PK11195 PET 显像结果显示,CFS 患者各脑区 BPND 平均值稍低于健康人但差异无统计学意义,其疲劳严重程度与尾状核 BPND 值呈负相关。利用靶向嘌呤能 P2X7 受体、环氧化酶和大麻素受体 2 等新型神经炎症示踪剂[20]有望进一步探索 CFS 中枢神经炎症机制。

3 中枢神经递质机制

CFS 存在神经递质系统异常[21]。神经递质失调与 CFS 临床表现密切相关,且是药物干预的关键;现有相关 PET 研究主要集中于 5-羟色胺、胆碱能、谷氨酸能和 γ-氨基丁酸能等神经递质。

5-羟色胺系统具有中枢调节作用,可能涉及 CFS 病理机制、影响疾病进程。^{11}C-(+)-McN5652 是 5-羟色胺转运蛋白的放射性配体;CFS 患者前扣带回皮质吻侧部 ^{11}C-(+)-McN5652 结合力显著降低[22]。^{11}C-WAY100635 PET 研究[23]显示 CFS 患者脑部 ^{11}C-WAY100635结合力普遍降低,以双侧海马为著。

胆碱能系统参与认知功能、快速眼动睡眠和运动控制等[24]。YAMAMOTO 等[25]通过 PET 观察血清毒蕈碱型乙酰胆碱受体(muscarinic cholinergic receptor, mAChR)自身抗体对 CFS 患者脑功能的影响,结果显示抗体阴性 CFS 组与对照组 BPND 无显著差异;相比上述 2 组,抗体阳性 CFS 组前额皮质、眶额区、前扣带回、颞叶、顶叶、枕叶皮质、纹状体、丘脑、杏仁核及脑干 BPND 降低,而抗体阴性与阳性 CFS 组间患者认知功能无显著差异。利用^{18}F-FEOBV[26]和^{18}F-ASEM[27]等新型胆碱能示踪剂可进一步观察中枢胆碱能系统与 CFS 症状的相关性,为 PET 研究 CFS 中枢神经系统机制提供更多选择。

不同神经递质系统之间的相互作用也是选择 PET 示踪剂的因素之一[28]。选择何种示踪剂及如何分析各指标之间变化的关联性对于阐释 CFS 中枢神经机制具有重要意义。谷氨酸能系统在支持高级认知功能方面发挥着核心作用。γ-氨基丁酸能系统代表脑部主要抑制性神经递质系统,对于调节认知控制和工作记忆功能振荡动力学具有重要作用。CFS 患者脑部谷氨酸能和 γ-氨基丁酸能系统可能存在异常。部分 CFS 患者血清乙酰肉碱水平减低,且与患者疲劳评分相关[29]。经乙酰肉碱治疗后,CFS 患者疲劳和注意力不集中症状有所改善[30]。2-^{11}C-acetyl-L-carnitine PET 成像显示 CFS 患者前额叶和颞叶皮质、扣带回和小脑乙酰肉碱摄取显著减少[31]。针对谷氨酸能系统的^{18}F-FPEB 和^{18}F-FIMX 及针对 γ-氨基丁酸能系统的^{11}C-flumazenil 已用于神经系统研究[32-34],有望直接观察 CFS 患者谷氨酸能和 γ-氨基丁酸能系统改变而改善对 CFS 中枢发病机制的理解并加速新型生物学

标志物和治疗方法的发掘。

4 中枢线粒体/能量代谢异常机制

中枢线粒体异常可能是 CFS 发病机制之一。CFS 患者血浆或周围组织中线粒体的脱氧核糖核酸、信使核糖核酸、代谢物和酶,以及线粒体呼吸功能等存在异常[35-46],而血液生物能量分析与脑部线粒体功能和代谢检测结果呈正相关[47]。线粒体呼吸链复合酶Ⅰ(mitochondrial respiratory complex Ⅰ, MCⅠ)是脑部生物能量学的重要调节器,可维持细胞钙稳态,产生活性氧和活性氮,以及调节细胞凋亡[48]。动物研究[49]发现 CFS 大鼠模型前额叶皮质 MCⅠ、Ⅱ、Ⅳ和Ⅴ活性显著降低。目前 CFS 线粒体功能障碍研究开展较少且设计多样,而生化实验结果易受多种因素影响,多依赖间接方法在体评估脑线粒体,其准确性有限。靶向 MCⅠ PET 可在一定程度上解决上述问题。^{18}F-BCPP-EF 示踪剂的研发,使非侵入性在体定量评估 MCⅠ活性成为可能[50],有利于动态观察 CFS 患者线粒体异常。此外,线粒体呼吸链的其他成分如复合酶Ⅱ~Ⅴ、泛醌和细胞色素 C 也可作为评估线粒体功能的合格靶点[51],如^{11}C-ubiquinol-10 和^{11}C-ubiquinone-10 可用于泛醌成像[52]。应加大力度针对以上靶点、尤其线粒体呼吸链复合酶Ⅴ研发示踪剂,以通过临床纵向研究全面观察 CFS 中枢线粒体异常。

5 小结

目前 PET CFS 研究存在示踪剂靶点覆盖面较窄、费用昂贵,对 CFS 病因学和病理生理学认识不足,缺乏标准化及结果质量不高等问题。可通过计算血脑屏障渗透率建模工具、结合高通量筛选提高效率以开发和验证示踪剂,加强开发中枢神经 PET 处理系统以提高图像分辨率、灵敏度并缩短扫描时间;以多中心、大数据、前瞻性研究进行多模态纵向跟踪分析,全面观察 CFS 脑葡萄糖代谢改变、神经炎症、氧化应激、神经递质异常和线粒体功能障碍之间的网络关系并进行细化研究。

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使用阿拉伯数字和汉字数字的一般原则

根据 GB/T 15835《出版物上数字用法的规定》

(1)在统计图表、数学运算、公式推导中所有数字包括正负整数、小数、分数、百分数和比例等,都必须使用阿拉伯数字。

(2)在汉字中已经定型的词、词组、成语、缩略语等都必须使用汉语数字,例如:一次方程、三维超声、二尖瓣、法洛四联症、星期一、五六天、八九个月、四十七八岁等。

(3)除了上述情况以外,凡是使用阿拉伯数字而且又很得体的地方,都应该使用阿拉伯数字。遇到特殊情况时,可以灵活掌握,但应该注意使全篇同一。

(4)如果数字的量级小于 1 时,小数点前面的零(0)不能省去,如 0.32 不能写成.32。