·指南与共识·

中国神经修复细胞治疗临床应用指南（2015年版）

中国医师协会神经修复学专业委员会
国际神经修复学会中国分会

一、前言

神经修复学是一门重要的临床医学和神经科学学科，其目的是修复或促进和维持神经功能和结构的完整性[1]。

国际神经修复学会北京宣言（2015年修定德黑兰版）宣布，“中枢神经系统损伤和神经退化后功能是可以恢复的”；并指出细胞治疗将可能成为神经修复学治疗策略的核心技术[1]；其基础研究已证实30余种细胞具有神经修复作用[2-58]。目前用于临床神经修复治疗的细胞可以分为三类，第一类为成熟和仍具有增殖能力的未成熟神经功能细胞，如神经祖（前体）细胞、嗅鞘细胞、雪旺细胞、少突胶质细胞和神经元等。第二类为基质或间充质类细胞，包括来自于骨髓、周围血或脐带血的单个核细胞及其分类和培养的细胞，来自于脐带和脂肪等间充质细胞。第三类为全能、多能或单能分化的干细胞，如胚胎干细胞和人类诱导多能干细胞等，这类细胞因其成瘤性和分化不可控性不能直接移植，故临床主要应用其衍生产品[59-60]。世界上30多个国家已经将第一、二类细胞应用于临床实践，安全性得到证实，大部分患者获得神经功能改善[61-95]。现阶段，本临床指南主要适用于第一、二类细胞的临床应用研究，作为第三类的干细胞临床研究应严格遵守国家卫计委发布的《干细胞制剂质量控制和临床前研究指导原则（试行）》和《干细胞临床研究管理办法（试行）》。

中国于2011年由国际神经修复学会中国分会制定发布了《中国神经修复细胞治疗临床规范》[96]，并于2012年修订发布了英文版《中国神经修复临床细胞治疗应用推荐标准》[97]，这些工作对推动这一领域规范治疗和建立世界性行业治疗指南具有重要意义，体现出中国神经修复学专家的专业技术追求和肩负的社会责任。基于目前基础研究和临床研究阶段性成果，今年中国医师协会神经修复学专业委员会暨国际神经修复学会中国分会再次广泛征求全国相关专家的意见和深入讨论，修订本指南的2012年版，在山东泰安召开的第二届年会上全会讨论表决通过。

鉴于科学技术发展迅速和根据国家相应政策法规，在基础研究、转化医学和循证医学临床研究的基础上，今后专委会仍将定期补充修定和更新内容，发布更新版本。

二、医院应具备的基本条件

1. 设施：具有符合国家相关标准及相关部门认定的细胞实验室和细胞产品质量控制的相关设备。

2. 人员：（1）细胞移植治疗医师（副主任医师及以上），应具备相关专业学会、协会细胞移植治疗技术系统培训并考核合格；（2）细胞制备实验室人员，负责人应具有副高级及以上专业技术职称；从事细胞制备的操作人员，必须经过细胞制备相关专业系统培训并考核合格；（3）从事质量检验的工作人员应具有相关专业大学（专）本科及以上学历，经专业技术培训并考试合格；（4）中国医师协会神经修复学专业委员会将积极承担神经修复细胞治疗的基地评定和相应专业技能培训。

三、条款

本指南包括神经修复细胞治疗指导原则、细胞名称、细胞质量控制、细胞剂量、患者知情同意、细胞治疗适应证、细胞治疗禁忌证、细胞治疗方法操作记录和要点、安全评价和疗效评价。

（一）神经修复细胞治疗的指导原则

适时、足量、多途径、多种细胞、多疗程和联合治疗。在循证医学和大数据的基础上，突出个性化优化治疗，不断探索精准医疗。

（二）细胞名称

细胞是生物体结构和功能的最基本单位，包括所有各种发育阶段和各种不同功能的细胞。从细胞发育时段上看，可分为干细胞和成熟前或成熟细胞，前者包括全能干细胞、多能干细胞和单能干细胞，后者包括发育不成熟的祖或前体细胞、成熟功能细胞

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和间充质细胞,干细胞和祖细胞之间最重要的区别是干细胞可以无限期复制,而祖细胞仅能有限复制,且只能分化成特定类型的细胞或靶向细胞。干细胞是细胞中的重要组成部分,鉴于目前将干细胞概念泛化或取代细胞用语已导致把干细胞治疗风险泛化为了整个细胞治疗的风险,因此在细胞治疗阐述中,应严格规范所用具体细胞的名称术语。

建议以含量最多的细胞类型命名并注明来源,如嗅黏膜嗅鞘细胞、雪旺细胞、脑神经祖(前体)细胞、嗅球嗅鞘细胞、骨髓单个核细胞、外周血单个核细胞、脐带血单个核细胞、脐带间充质细胞和脂肪间充质细胞等。

(三) 细胞质量控制

质量可控性是细胞治疗安全性和有效性的基础,整个流程包括:细胞采集、培养、鉴定、扩增、各种细胞因子成份及含量检测、细胞代数、外源因子、储存、生物学效力(活力、增殖力)检测、运输、临床使用前处置和临床移植治疗操作等环节及因素。建议无血清培养或者采用必要措施清除或洗净胎牛血清。质控指标至少应包括:细胞总数、体外培养代数、细胞纯度、细胞活率(不低于 95 %)、生物学效力(不低于 80 %)、特殊表面标记比例、传染病指标以及内毒素等检测指标。在一定低温条件下,裸细胞自临床实验室至移植应用到患者的最佳时限不超过 2 h[98]。

(四) 细胞剂量

细胞使用必须达到有效剂量,且不能超出安全剂量。每种细胞、每种移植途径、单次及累积有效剂量和安全剂量有一个范围,对于不同疾病,也存在一定差异。每次(靶点)注射细胞悬液最大体积:脑实质内 200 μl、脊髓实质内 25 μl[99]、脑脊液途径 10 ml、血管途径 10 ~ 100 ml。目前推荐常用细胞单次剂量处方如下。

1. 胶质细胞,如嗅鞘细胞和雪旺细胞:(2.0 ~ 3.0) ×10^6 鞘内注射;(1.0 ~ 2.0) ×10^6 脊髓实质内注射;(2.0 ~ 4.0) ×10^6 脑实质内注射。

2. 神经祖(前体)细胞:(5.0 ~ 6.0) ×10^6 鞘内注射;(5.0 ~ 6.0) ×10^6 脊髓实质内注射;1.0 × 10^7 脑实质内注射。

3. 脐带间充质细胞:(0.4 ~ 0.5) ×10^6/kg 体重,静脉输注,老年体弱者酌情减量 1/3 ~1/2;(5.0 ~ 10.0)×10^6脊髓实质内注射;1.0 × 10^7脑实质内注射;(5.0 ~ 6.0) ×10^6 鞘内注射。

4. 脐带血单个核细胞:(1.0 ~ 2.0) ×10^6/kg 体重静脉输注,老年体弱者酌情减量 1/3 ~ 1/2;(5.0 ~ 6.0) ×10^6 鞘内注射。

5. 骨髓单个核细胞:(3.0 ~ 9.0)×10^8 静脉输注;(5.0 ~ 6.0) ×10^6 鞘内注射。

6. 动员后的外周血单个核细胞:自体可采用由血细胞分离机处理循环血液所得的有核细胞 1.0 × 10^9 静脉输注。

(五) 患者知情同意

患者及其家属有权利知晓与细胞及细胞移植操作有关的所有利弊和风险。医生应不断学习和掌握最新的细胞治疗相关知识,如实客观解答和解释。

(六) 细胞治疗适应证

神经系统疾病和损伤,包括:神经创伤、神经退变、缺血性或缺氧性脑损伤、脱髓鞘、感觉运动障碍性疾病、神经性疼痛以及中毒、物理和化学因素、免疫、传染、炎症、遗传性、先天性、发育性和其他原因导致的神经系统损害。

(七) 细胞治疗禁忌证

全身情况较差或主要脏器功能障碍等不能耐受治疗;手术部位有感染;有出血倾向或伴有凝血功能障碍无法纠正;精神异常等。超敏体质、超高龄(> 90 岁)和妊娠等慎用。

(八) 细胞治疗方法操作记录和要点

细胞治疗方法操作记录包括麻醉方式、移植入路、手术方式、移植方式、移植部位、移植细胞类型和移植细胞数量、浓度及体积等。

治疗方法记录举例如下:(1) 局麻下经额部入路立体定向脑实质内(× 靶点)神经祖(前体)细胞移植术;(2)局麻下经侧脑室穿刺 ×× 细胞移植术;(3)局麻下经小脑延髓池穿刺 ×× 细胞移植术;(4) 局麻下经皮(颈椎、胸椎、腰椎)穿刺鞘内 ×× 细胞移植术;(5)局麻下经皮穿刺、经 X 线引导蛛网膜下腔 ×× 细胞移植术;(6) 全麻下脊髓实质内 ×× 细胞移植术;(7) 局麻下 CT 椎管造影引导脊髓实质内 ×× 细胞移植术;(8) 局麻下 CT 椎管造影引导脊髓蛛网膜下腔 ×× 细胞移植术;(9) 局麻下 CT 引导脊髓实质内 ×× 细胞移植术;(10) 局麻下 CT 引导脊髓蛛网膜下腔 ×× 细胞移植术;(11)经静脉 ×× 细胞治疗;(12) 经血管内超选择插管 ×× 动脉内 ×× 细胞移植术;(13) 肌肉内 ×× 细胞移植术。

不同的细胞应有最佳的治疗途径,目前首选的操作要点[100]:

脑部病变(颅脑损伤、卒中等):需将细胞注入到病灶周缘,其他非特异性或弥漫性病变(如脑性瘫

痪、肌萎缩侧索硬化等),应将细胞注入到神经修复网络关键点,标准解剖定位在侧脑室体部前 1/4~1/3 旁,中线旁开 23 ~ 27 mm,主要为额叶放射冠锥体束走行处,同时为多条投射纤维、联合纤维和连合纤维的会聚处。

脊髓病变 :应将细胞微创注射到病变与上下正常组织交界处的脊髓内。

周围神经病变 :应将细胞注入到病变处。

(九) 安全评价系统

采用规范术语,详细记录任何与细胞治疗相关的不良事件,例如发热、头痛、恶心、呕吐、厌食、感染、皮疹、切口愈合障碍、呼吸困难、血压和心率异常、神经功能恶化、脑脊液漏以及抽搐等。

(十) 疗效评价系统

对不同疾病分别采用国际最常用的统一标准或量表进行评价(具体参考 Neurorestoratology[100]、中枢神经修复学 [101] 及相关专著)。中国医师协会神经修复学专业委员会将定期开办全国培训班,对参与评价的医生进行统一培训,考核合格后,颁发合格证书。

(十一) 个性化治疗和客观检查资料收集

必须在规范化的基础上探索个性化治疗,不断提高疗效。建议治疗前后,精确收集患者信息,包括脑功能磁共振、脑或脊髓 DTI、周围神经磁共振神经成像和神经电生理检查等客观检查。

(十二) 细胞治疗基本原则和多中心研究

根据既往临床实践积累,多类型的细胞联合、途径联合、疗程设定和联合其他神经修复策略治疗,是目前研究的主要方向,学会将定期组织修订和公布安全方案和增效方案。学会也将积极组织多中心对不同疾病的治疗研究(对适合做随机、双盲和对照研究的课题,应优先安排 ;对不适合的,应积极开展其他类型的临床研究)。

(十三) 发表义务

对于神经修复细胞治疗的各种临床研究结果,各治疗单位应及时分析总结,公开发表,以供国内外其他研究者参考、对比和进一步验证。

四、建立中国神经修复细胞治疗登记系统(CNRCTRS)

1. 目的和意义 :为了促进细胞移植治疗科学化、规范化管理和整合临床科研资源,本专业委员会将尽快建立中国神经修复细胞治疗信息报告管理网络系统,为临床医生和国家主管部门提供及时、准确的监测信息,并适时制定风险控制预案。

2. 方法 :凡开展神经修复细胞治疗的相关医疗单位均应加入并共享资源,由专业委员会制订、建立共享网络平台,资料保密性由专业委员会负责。采用网络直报方式,对于每一例接受细胞治疗者,按统一格式(专业委员会提供) 详细记录,包括患者基本信息、疾病诊断、患病或损伤时间、移植细胞种类和名称、移植方式、移植数量、移植次数、治疗前及治疗后,随访(时间) 功能评价资料、安全(不良事件) 报告和患者存活时间等。

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