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综述

急性淋巴细胞白血病儿童认知功能损害的临床研究进展

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［摘要］急性淋巴细胞白血病（acute lymphoblastic leukemia，ALL）是儿童期最常见的恶性肿瘤性疾病。随着临床诊治水平的不断提高，获得完全缓解后长期生存的ALL儿童越来越多，其中相当部分患儿都存在认知功能损害，并对学习、就业和社交活动产生严重的不良影响。该文从ALL患儿认知功能损害的影响因素、检测技术的应用及预防与治疗对ALL患儿认知损害的临床研究进展进行综述。

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［关键词］急性淋巴细胞白血病；认知功能；影响因素；儿童

Recent research on cognitive impairment in children with acute lymphoblastic leukemia

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Abstract: Acute lymphoblastic leukemia (ALL) is the most common malignant neoplastic disease in children. With the continuous improvement in diagnosis and treatment, there has been an increasing number of ALL children who achieve long-term survival after complete remission; however, a considerable proportion of these children have cognitive impairment, which has a serious adverse impact on their learning, employment, and social life. This article reviews the latest research on cognitive impairment in children with ALL from the aspects of the influencing factors, detection techniques, and prevention/treatment methods for cognitive impairment.

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Key words: Acute lymphoblastic leukemia; Cognitive function; Influencing factor; Child

急性淋巴细胞白血病（acute lymphoblastic leukemia，ALL）是儿童期最常见的恶性肿瘤性疾病。随着临床多中心协作组的开展和化疗方案的不断改善，我国ALL患儿的5年总体生存率达到90%[1]。这意味着长期获得完全缓解的ALL患儿数量在不断增加。然而，我国上海地区傅晓燕等[2]的研究结果显示长期无病生存5年以上的ALL患儿的总智商、言语智商及操作智商均显著低于健康对照组。圣裘德儿童研究医院通过父母问卷调查也发现30%~60%的ALL患儿会发生迟发性认知障碍，主要表现为记忆力、注意力及执行功能受损[3]。此外，ALL患儿的学业完成度及就业率也明显低于兄弟姐妹及其他健康对照组[4]。ALL患儿的神经认知功能损伤已成为不可忽视的健康问题和社会问题。因此，本文从ALL患儿认知功能损害的影响因素、相关检测技术的应用及预防与治疗进行综述。

1　ALL患儿认知功能损害的影响因素

1.1　初诊年龄

研究发现儿童认知能力的发展与大脑皮层发

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育成熟的先后顺序一致[5]。Gogtay 等[5]对 13 名儿童的大脑皮层发育进行了长达 8~10 年的随访研究，结果发现与基本功能（如感觉、运动）相关的大脑皮层最早成熟，然后是与空间导向和语言发展相关的颞顶叶皮层，最后才是与执行功能、注意力及协调动作相关的前额叶和外侧颞叶皮层。Hardy 等[6]对 192 例结束化疗 8~24 个月的 ALL 患者的研究发现，与初诊年龄≥10 岁的患儿相比，<10 岁的患儿总体智商（95.0 vs 106.7，P<0.001）和处理速度评分（93.5 vs 98.6，P=0.02）明显降低。初诊年龄小的 ALL 患儿，白血病细胞的浸润及化疗药物的细胞毒性作用对神经系统发育的影响更大，记忆力、注意力及执行功能等未发育成熟的高级神经认知功能更容易受损[7-9]。

1.2 患儿性别

多项研究显示女性是 ALL 患儿化疗后神经认知功能损害的危险因素[10-12]。Partanen 等[10]分别在诱导、再诱导、结束化疗时、结束化疗后 2 年 4 个不同时间段对 ALL 患儿进行神经认知功能测试的纵向研究，结果发现与男性患儿相比，女性患儿的注意力在接受化疗后更容易受损。van der Plas 等[12]的研究显示化疗后女性患儿的情绪调节能力及记忆力比男性患儿更差。其病理生理机制可能与性激素的作用及男、女在不同脑区的髓鞘形成率、树突修剪和脑血管发育不同有关[13-14]。长期研究结果表明，与同胞兄弟姐妹相比，女性 ALL 患儿完成的学校教育年限更少、失业率更高且收入更低，但这不能排除社会因素的影响与干预[15-16]。

1.3 临床危险度分型及化疗药物

临床危险度分型在指导 ALL 患儿治疗及提示预后方面有重要意义。研究显示中/高危临床危险度分型是 ALL 患儿神经认知功能的危险因素[17-18]。Jacola 等[18]发现中/高危组 ALL 患者的总智商、工作记忆、处理速度及学习成绩明显低于低危 ALL 患儿组，造成这种差别的原因除了疾病本身外，还与各组间的化疗方案及药物累积剂量的差别有关。

目前全身强化静脉化疗和鞘内注射已经取代颅脑放疗，成为预防和治疗中枢神经系统白血病的主要手段[3, 19]。Kull 等[3]根据是否接受颅脑放疗及放疗剂量将 ALL 患者分为单纯化疗、18 Gy 放疗、24 Gy 放疗组，发现虽然这 3 组患儿的执行功能（15.9% vs 23.0% vs 31.7%）、注意力（14.5% vs 21.5% vs 31.1%）、记忆力（13.1% vs 18.7% vs 30.6%）严重受损的比例随放疗剂量的增加而增加，但单纯化疗组 ALL 患儿仍然存在不可忽视的认知损害。ALL 常用的化疗药物大多是细胞毒性药物。大量研究[20-21]发现大剂量氨甲蝶呤（methotrexate，MTX）能影响脑白质髓鞘化进而影响脑白质完整性，并被认为是神经认知障碍发生的重要危险因素。MTX 可逆地抑制二氢叶酸还原酶，并导致 5-甲基四氢叶酸减少。5-甲基四氢叶酸是循环叶酸的主要形式，也是同型半胱氨酸再甲基化为甲硫氨酸的共底物。甲硫氨酸对脱氧核糖核酸甲基化至关重要。脑细胞 DNA 甲基化的改变可能是 MTX 治疗相关的神经毒性和长期存活者的神经认知功能损害的机制之一。并且同型半胱氨酸和兴奋性氨基酸的积累可能对内皮细胞有毒性，并使神经元对氧化损伤敏感，最终导致髓鞘合成减少和神经元死亡[22]。同时，糖皮质激素可通过降低谷胱甘肽过氧化物酶的活性进而影响脑细胞抗氧化能力[23]。当 MTX 与糖皮质激素合用时会对脑细胞的抗氧化能力造成双重打击。研究发现糖皮质激素受体分布多的脑区域（海马和小脑）出现体积缩小及相关脑区功能减弱[24-25]。van der Plas 等[12]的研究显示记忆力的损伤与鞘内注射 MTX 次数及地塞米松的使用剂量有关。虽然目前缺少其他化疗药物与 ALL 患儿神经认知功能的相关性研究，但有中枢神经系统毒性的病例报道，如大剂量阿糖胞苷可引起白质脑病症状[26]，左旋门冬酰胺酶可引起癫痫、头痛及局灶性脑功能缺陷症状[27]。长春新碱除了引起最常见的周围神经病变，也可引起颅神经病变，导致视力及听力障碍，一些患者甚至可发展为上行性麻痹及脑病[28-29]。这些疾病通常容易并发或继发神经认知功能的损伤。

1.4 其他相关影响因素

主要照料者文化程度、家庭经济水平、家庭功能、社会医疗保险制度的类型及等级均可能对 ALL 患儿的神经认知功能产生影响[6, 17]。有研究[30]发现日常居住面积<55 m^2 与记忆力受损及处理速度降低相关，家庭功能差与执行功能障碍相关。尽管这些因素作用机制不清楚，但对于临床工作者发现高危对象具有一定参考意义。

2 检测技术在 ALL 儿童认知功能的应用

2.1 MRI 脑成像技术

磁共振成像（magnetic resonance imaging，MRI）在显示脑灰白质的结构方面有其独特的优

势。基于体素的形态学测量是目前最常用的一种全脑分析技术。研究显示经过化疗的ALL患者的颅脑MRI可见脑体积缩小及皮质变薄。Phillips等[24]使用薄层MRI成像技术发现化疗结束5年后ALL患儿的双侧小脑、海马、颞叶、额叶和顶叶的体积持续性变小。此外，颅脑MRI结构改变也被证明与认知功能损伤表现相对应[31]，如总白质体积的减少与学业成绩、智力和注意力降低相关，额叶和颞叶总体积与数学、阅读、词汇和记忆跨度有关，杏仁核、丘脑、纹状体和胼胝体的白质体积与工作记忆相关。

弥散张量成像是通过检测水分子扩散自由度及方向来量化脑白质微观结构的MRI技术，可反映纤维束数目、密度及髓鞘化程度。Follin等[32]发现ALL患者穹隆、双侧扣带、右钩束的各向异性系数降低，左侧扣带、双侧钩束的横向扩散系数增加，这些都提示脑白质微观结构的受损。此外还发现穹窿的改变与言语记忆受损有关，穹窿、钩束和扣带的改变与视觉记忆受损有关。

磁共振波谱成像是目前唯一利用化学位移现象来检测活体组织代谢产物的无创方法。N-乙酰天冬氨酸主要存在于神经元内，其浓度可反映神经元的密度及功能状况。与磷脂代谢相关的胆碱可反映髓鞘的完整性。有研究发现化疗后ALL患儿的N-乙酰天冬氨酸/肌酸比值及N-乙酰天冬氨酸/胆碱比值下降，胆碱/肌酸比值增加[33-34]。这些代谢产物的变化提示着神经元受损的可能。

功能磁共振成像（functional magnetic resonance imaging，fMRI）通过测量血流动力学及局部耗氧量来反映神经元的活动，分为静息态和任务态两种类型。研究发现ALL患儿的大脑静息态信号激活总面积显著低于健康儿童[35-36]。Fellah等[21]在持续性操作测试时对ALL患儿进行任务态fMRI检查，发现初诊年龄小与双侧顶颞叶皮层激活低有关，MTX累积剂量高与双侧额、顶叶和右侧颞叶激活低有关。这也再次验证了初诊年龄小和大剂量MTX暴露是神经认知功能损害的危险因素。

总之，ALL患儿的大脑解剖结构、功能及代谢水平在结束化疗后都发生了一定程度的改变，特别是在额叶、海马和其他涉及学习、记忆和执行功能的区域，并与神经认知功能测试受损的能区相对应。多模态MRI技术的发展为进一步了解ALL患儿认知功能损伤的机制及结构解剖基础提供了更多可能。

2.2 脑脊液中神经化学标记物检测

肿瘤治疗期间的脑脊液生物标志物变化与后期的神经认知功能存在相关性[37-38]。一项研究[39]发现ALL患儿治疗期间反映星形胶质细胞增生的胶质纤维酸性蛋白、反映髓鞘降解的髓鞘碱性蛋白、反映神经元损伤的总tau蛋白水平增加与5年后白质脑病风险增加及额叶表观弥散系数降低有关。Elens等[40]的研究显示治疗期间脑脊液磷酸化tau蛋白水平增加与化疗后智力呈负相关（r=–0.414，P=0.04）。诱导和巩固治疗后脑脊液中氧化磷脂酰胆碱水平升高与随访时工作记忆较差有关[41]。尽管以上这些初步证据受到小样本量的限制，但这些发现表明反映中枢神经系统细胞完整性、氧化应激及炎症的脑脊液生物标志物有助于识别白血病患儿远期神经认知的风险个体，以便早期干预。

2.3 化疗药物相关的基因多态性检测

目前儿童ALL的治疗主要依赖于化学药物治疗。化学药物的药代动力学及药效学相关基因的遗传变异与ALL患儿的神经认知功能明显相关[42]。单核苷酸多态性检测是目前最常用于检测遗传变异的技术。Elens等[43]发现亚甲基四氢叶酸还原酶（methylenetetrahydrofolate reductase，MTHFR）1298CC基因型患儿在诱导期鞘注MTX后脑脊液磷酸化tau蛋白水平较AA/AC基因型明显升高，且与成年后操作智商降低有关。Kamdar等[44]研究结果显示丝氨酸羟甲基转移酶（serine hydroxymethyltransferase，SHMT）1420C>T、蛋氨酸合成酶（methionine synthase，MS）2756A>G、蛋氨酸合成酶还原酶（methionine synthase reductase，MTRR）66A>G和胸苷酸合成酶（thymidylate synthase，TS）也与ALL患儿的神经认知损伤有关，且≥6个叶酸代谢途径风险等位基因的ALL儿童比<6个风险等位基因的ALL儿童的神经认知功能表现更差。溶质载体有机阴离子转运蛋白家族成员1B1（solute carrier organic anion transporter family member 1B1，SLCO1B1）是一种主要表达在肝脏的载体。*SLCO1B1*中的rs11045879 CC基因型被证明与MTX血药浓度显著相关，并能使神经认知功能损害的危险性提高[45]。尽管有大量关于MTX的药物遗传学研究，但目前没有明确建议在MTX治疗前进行药物遗传学检测。其他化疗药物与神经认知相关的基因组学尚有待进一步研究。

3 预防与治疗

哌甲酯及其衍生物作为治疗6岁以上注意力缺陷多动障碍（attention deficit hyperactivity disorder，ADHD）儿童的一线临床用药，也被用于治疗继发性脑损伤患儿的注意力缺陷[46]。Conklin等[47]研究显示哌甲酯改善白血病患儿的注意力缺陷症状的有效率低于既往文献报道[48]治疗单纯ADHD的有效率，且发现伴有智力低下患儿的症状缓解率更低。这可能与ALL儿童合并更多的学业问题及神经损伤有关。也有报道[49]显示哌甲酯能改善肿瘤患儿的疲劳症状及产生积极情绪效应。多奈哌齐作为乙酰胆碱酯酶抑制剂，能帮助改善成人肿瘤患者的记忆力及语言表达，但在ALL患儿中的疗效及安全性尚不明确[50-51]。总体而言，药物治疗因其药物类型限制及不良反应对于患儿及家属来说可接受性不强。

药物治疗虽能改善某些临床症状，但大多数认知障碍症状的改善主要依赖于非药物治疗。因为干预方向和方式的多样化，有必要在干预开始前对患儿进行智力评估及关键认知能区的能力检测，以确保所实施的干预与患儿的能力水平相匹配。以游戏为主要形式的认知训练对于小年龄儿童很有必要，但要注意结合患儿自身能力计划训练的方向及强度[52]。对于年龄偏大的患儿，可进行针对性的技能训练，如书写训练、阅读训练及生活技能训练。此外，父母培训及家庭治疗有利于加强父母对疾病的认识、增强治疗依从性及培养正确的教养方式[53]，如家庭奖赏制度可以加强患儿的行为管理，减少不良行为发生的频率[54]。学校是学龄期儿童生活学习的主要场所，以融合教育为代表的个体化教学也是干预的重要环节。此外，健康的饮食习惯，尤其是体育锻炼对白血病患儿来说是有益的，可以预防或减轻心血管和代谢的晚期影响[55]，最终可能有助于改善神经认知功能。

综上所述，白血病患儿发生认知障碍的机制尚未明确。疾病及化疗药物使白血病患儿的神经发育损伤更明显，临床表现更加复杂，在治疗上面临更大的挑战。关于改善或预防ALL患儿神经认知损害的策略研究尚处于早期阶段，未来的研究方向主要集中于继续改进中枢神经系统靶向化疗方案，并寻找早期干预的心理教育工具及新型药物治疗。

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