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综述

先天性心脏病相关性神经发育障碍的研究进展

刘玉梅¹ 刘天钰² 综述 农绍汉¹ 周晓光² 审校

(1. 南方医科大学附属广东省人民医院(广东省医学科学院) 新生儿科, 广东广州 510080;

2. 中山大学附属第八医院新生儿科, 广东深圳 518033)

[摘要] 儿童神经发育障碍发生率与致残率均较高, 已成为影响全球儿童健康的重大公共卫生问题。先天性心脏病患儿神经发育障碍 (congenital heart disease associated neurodevelopmental disorder, CHDNDD) 尤为常见, 不同先天性心脏病类型、手术方式、年龄阶段, 以及发生不同并发症或合并症时其临床特点各有不同。近年来, 基于“早期诊断、早期治疗”的干预模式, 国外开始探讨高危儿神经发育障碍的预防性早期干预新技术, 并取得较好效果。该文就CHDNDD临床特点进行综述, 以期为先心病患儿正确进行预防性早期干预新技术提供理论依据, 从而进一步降低CHDNDD发生率。 [中国当代儿科杂志, 2024, 26 (11): 1231-1237]

[关键词] 神经发育障碍; 先天性心脏病; 随访; 预防性干预; 儿童

Research progress on neurodevelopmental disorders associated with congenital heart disease

LIU Yu-Mei, LIU Tian-Yu, NONG Shao-Han, ZHOU Xiao-Guang. Department of Neonatology, Guangdong Provincial People's Hospital & Guangdong Academy of Medical Sciences, Southern Medical University, Guangzhou 510080, China (Nong S-H, Email: nongsh98@hotmail.com)

Abstract: The incidence and disability rate of neurodevelopmental disorders in children are high, making it a significant public health issue affecting children's health globally. Neurodevelopmental disorders are particularly common in children with congenital heart disease (CHD), with clinical characteristics varying by type of CHD, surgical approach, age stage, and the presence of different complications or comorbidities. In recent years, based on the intervention model of "early diagnosis and early treatment," foreign studies have begun to explore new techniques for preventive early intervention in high-risk children with neurodevelopmental disorders, achieving promising results. This paper reviews the clinical characteristics of neurodevelopmental disorders associated with CHD, aiming to provide a theoretical basis for implementing new preventive early intervention techniques for children with CHD, thereby further reducing the incidence of neurodevelopmental disorders associated with CHD.

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Key words: Neurodevelopmental disorder; Congenital heart disease; Follow-up; Preventive intervention; Child

全球先天性心脏病 (congenital heart disease, CHD) 患病率约为 9/1 000 活产婴^[1], 随着医学科学的发展, CHD 患儿成活率明显升高, 先天性心脏病患儿神经发育障碍 (congenital heart disease associated neurodevelopmental disorder, CHDNDD) 也逐渐增加^[2-3], 其患病率高达 44%^[2]。神经发育障碍 (neurodevelopmental disorder, NDD) 已成为影

响全球儿童健康的重大公共卫生问题^[4], 在中低收入国家尤其严重^[5]。CHDNDD 常表现为运动、认知、语言发育障碍, 社会适应能力及心理行为等方面的异常或障碍, 不同 CHD 类型、不同手术方式、不同年龄阶段, 以及发生不同并发症或合并症时其临床特点各有不同, 并可延续至学龄期、青春期^[6], 甚至成年期。近年来随着预防性早期

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[作者简介] 刘玉梅, 女, 博士, 副主任医师。

[通信作者] 农绍汉, 男, 主任医师。Email: nongsh98@hotmail.com。

干预 (preventive early intervention strategy, PEIS) 技术悄然兴起, CHDNDD 和脑性瘫痪 (cerebral palsy, CP) 发生率有所下降^[7]。本文就不同情况下的 CHDNDD 临床特点进行综述, 以期对 CHD 患儿正确进行 PEIS 提供理论依据。

1 流行病学

全球 CHD 患病率持续升高, 在 1996—2005 年期间瑞典曾高达 20/1 000 活产婴^[8]。3~21 岁 CHD 儿童和青少年 NDD 患病率高达 20%~60% (平均 44%), 其中注意缺陷多动障碍 (attention deficit hyperactivity disorder, ADHD) 占 27.3%, 孤独症谱系障碍 (autism spectrum disorder, ASD) 占 9.6%, 智力发育障碍 (intellectual developmental disorder, IDD) 占 5.9%; CHDNDD 诊断年龄以学龄期最多^[2-3], 而 ASD 的平均诊断年龄为 34 个月, 远早于一般人群^[9], 并以男性更多见; 4~9 岁单纯性 CHD 患儿 NDD 发生风险增高 5 倍, 复杂性 CHD 增高 7 倍^[10]; 危重型 CHD 患儿 CP 患病率高达 1.5%^[11]; 4~17 岁诊断患有或应用药物治疗焦虑或抑郁的 CHD 患儿高达 18.2%^[10]。

需要进行体外循环手术者较不需要者 NDD 风险增高^[3], 有主动脉阻断史者以 ASD 更多见, 合并基因缺陷者, 更易发生 IDD^[2]。

2 病因与发病机理

CHDNDD 原因 70% 为先天性因素, 30% 为后天性因素^[12], 包括胎儿、围生期、社会和家庭因素^[1, 13]。

2.1 宫内脑结构改变

与正常对照组比较, CHD 胎儿脑总容量和局部脑容量减少^[14], 包括脑灰质、皮质下、小脑和脑干等脑容量减少^[15-16]。而危重型 CHD 胎儿大脑无髓鞘白质减少, 脑外和脑室内脑脊液 (cerebrospinal fluid, CSF) 增加, 并随胎龄增加, 无髓鞘白质/总脑容量比值降低, 大脑皮质/总脑容量比值和小脑/总脑容量比值升高, 脑室内 CSF/颅内容积比值及脑外 CSF/颅内容积比值降低; 但至新生儿期, 脑室内 CSF/颅内容积比值、脑外 CSF/颅内容积比值则随胎龄增加而升高^[15, 17]。部分 CHD 胎儿大脑额叶前后径短, 大脑额叶前后径/枕额径比值较小^[18]。研究表明, 脑容量减少是进行

体外循环手术 CHD 新生儿预后不良的生物标志物之一^[14], 是 CHD 患儿 2 岁时 NDD 的强有力独立预测因素^[12]。

CHD 胎儿脑结构改变一般始于胎龄 30 周, 并持续至出生, 甚至儿童期与青春期^[19]。复杂性 CHD 胎儿可能始于妊娠第 7 个月, 而危重型 CHD, 如法洛四联症 (tetralogy of Fallot, TOF) 和大动脉转位 (transposition of great arteries, TGA), 则可能始于妊娠第 4~6 个月^[18]。这些可能是 CHD 胎儿潜在的干预时间窗。

2.2 出生后脑结构改变

CHD 患儿出生后脑总容量和局部脑容量减少^[14], 包括总脑灰质容量、深部脑灰质、脑白质和海马颞区容量减少, 以及脑部各向异性分数降低^[20-21]。危重型 CHD 患儿脑发育障碍, 易致缺氧缺血性损伤, 与健康对照组比较, TOF 青少年右脑半球脑沟折叠模式改变^[22]。双心室患儿总脑容量减少 54 mL, 脑白质减少 40 mL, 脑干减少 1.2 mL^[23]。

手术也会加重 CHD 患儿神经损伤^[24]。儿童期手术治疗的单纯性 CHD 患儿, 成年后顶叶、颞叶、枕叶微结构组织成分改变, 右侧视觉皮质、梭状回与舌回枕部张量簇平均峰度发生显著特异性改变, 左脑半球脑沟折叠模式改变, 房间隔缺损患儿发生于左颞叶, 室间隔缺损患儿发生于整个左脑半球^[25-26]。

不同类型 CHD 患儿出生后以不同术式进行手术, 脑结构改变也会有所不同。进行体外循环手术的单心室新生儿, 脑灰质和白质容量减少, 而 CSF 体积增多^[27]。进行 Norwood 或 Hybrid 手术的左心发育不良综合征 (hypoplastic left heart syndrome, HLHS) 患儿, 术后 2 年脑容量减少, 以 Norwood 术式手术者更明显^[28]; 而进行 III 期 Fontan 手术者总脑容量、总脑灰质容量、深部脑灰质和脑白质容量减少^[20, 29]。

2.3 胎盘微结构与功能改变

CHD 胎儿胎盘微结构、灌注与功能可发生胎盘绒毛成熟延迟、胎盘重量降低、胎盘血流灌注不足, 以及慢性炎症等改变^[30], 导致胎儿脑皮质、深部灰质、脑干、小脑和总脑容量减少^[31]。

2.4 基因变化

研究发现, 不少 CHD 新生儿伴有 NDD 相关基因缺陷^[32], 而伴有基因缺陷的 CHD 新生儿, 神经损伤更明显^[24]。

2.5 其他

CHD患儿早产、手术时间延长、术后发生并发症和住院时间延长等均可增加NDD风险^[19, 24, 33]。

3 临床表现

3.1 常见临床表现

NDD是一组疾病谱，包括IDD、发育性言语或语言障碍（developmental speech or language disorder, DSD）、ASD、发育性学习障碍（developmental learning disorder, DLD）、ADHD、抽动障碍（tic disorder, TD）和其他^[7]。

CHD患儿在成长各个阶段均可能发生认知能力受损，包括注意力缺陷、执行能力与空间推理能力下降，以及社会心理发育障碍，易发生精神健康问题，尤其是焦虑和抑郁^[6]。CHDNDD发病高峰期是儿童早期^[34-35]，可导致TD、CP，或表现为运动能力下降，认知能力受损和心理行为障碍。运动能力下降主要表现为大运动与精细运动下降、发育性协调障碍、运动综合评分偏低和处理速度受限^[36-37]。认知能力受损主要表现为语言发育障碍，记忆力下降，注意力缺陷，解决问题能力、适应能力和执行能力下降，以及视空间处理、视运动整合和视空间技巧能力受限，导致智商（intelligence quotient, IQ）下降，学业成就较低^[3, 36, 38]。语言发育障碍常表现为言语、语言组词与语言发育等特定学习障碍，如接受与表达语言的能力下降、发音障碍等^[39]。心理行为障碍包括ASD、ADHD、社会交往能力下降、适应不良、行为与情感混合障碍、破坏性或攻击性行为，以及焦虑、抑郁、社会功能紊乱和非典型行为等精神疾病^[1, 35, 40]。

3.2 不同CHD类型的NDD临床特点

CHDNDD儿童和青少年主要表现为ADHD、ASD和IDD^[2]；单纯性CHD患儿手术后，成年时常见认知能力受损和心理行为障碍，如IDD，语言理解、知觉推理和视空间能力较差，记忆力和全面学习能力发育延迟，执行力下降，社会认知能力迟缓，ADHD和精神疾病^[38]。

无心力衰竭（heart failure, HF）的发绀型CHD患儿，IQ较低；需要进行体外循环手术的CHD儿童NDD主要表现为认知能力受损和情感问题，临床上常表现为社会交往困难，注意力缺陷和执行

功能下降^[3]。

危重型CHD患儿认知能力和运动能力较差，语言组词评分较低^[14, 41]；CP患病率可高达1.5%，表现为单侧痉挛性CP和IDD^[11]。复杂性CHD患儿认知能力和运动能力较差，常见内化（如焦虑、抑郁）或外化（如攻击、多动）行为问题，学业成绩较差，常需要特殊教育服务^[1]。TOF患儿常见神经认知能力缺陷，执行能力、视空间技巧、记忆力、注意力、社会认知能力和解决问题能力下降，学业成绩较差，以及睡眠障碍、ADHD、焦虑与破坏行为等精神疾病风险增高^[22, 34, 42]。单心室患儿常见认知与运动综合评分偏低，语言综合评分和IQ显著降低^[20, 39, 43]。TGA患儿常在执行能力、精细运动、注意力、工作记忆、视空间技能、高级语言技能和学业方面表现较差，而ADHD和精神疾病发生率较高^[1, 40, 44-45]。双心室患儿在社会交往中语言能力表现较差^[23]。HLHS患儿社会适应能力较差^[46]。

3.3 不同年龄阶段的CHDNDD临床特点

CHD患儿在成长各个阶段均可见认知能力受损和社会心理发育障碍^[6]；但不同年龄阶段，均有不同的临床特点。婴幼儿期多见肌张力下降，大运动、精细运动发育落后，语言和认知能力下降^[36, 41]，临床上常表现为ASD、注意力缺陷、言语与语言发育落后，尤其是感受性语言和表达性语言方面，同时其视空间处理、视运动整合及社会交往能力下降^[1, 9]。学龄前期常见大运动、精细运动发育迟缓，认知和社会适应能力下降^[37]，较多表现为言语和语言发育迟缓、ADHD^[45]、记忆力下降、注意力缺陷、解决问题能力和交流技巧较差^[47]，以及焦虑和抑郁^[1]。学龄期主要表现为ADHD、ASD、IDD^[2]，在执行能力、精细运动、注意力、工作记忆、视空间技能、高级语言技能及学业方面表现较差，精神疾病发生率较高^[40, 44]。成年后，IQ较低，语言理解、知觉推理、工作记忆能力和视空间能力较差，全面学习能力、执行力和处理速度下降，社会认知能力发育迟缓，ADHD、精神健康问题突出^[35, 38, 48]，以及癫痫风险增加。

3.4 不同CHD类型在不同年龄阶段的临床特点

TOF患儿在婴儿期和儿童早期，大运动、精细运动和认知能力下降；到青少年期，常见认知能力缺陷、睡眠障碍、ADHD、焦虑及破坏行为等精神疾病^[22, 34, 42]。单心室患儿，Fontan术前常见认

知与运动综合评分偏低，语言综合评分显著降低^[39]；而在 Fontan 术后语言评分和 IQ 可能更低^[20, 43]。TGA 患儿在婴幼儿期适应能力不足，易出现言语与语言发育迟缓和 ADHD^[1, 44]，到儿童和青少年期，常在执行能力、精细运动、注意力、工作记忆、视空间技能和高级语言技能方面表现较差，学业成就较低，精神疾病较突出^[40, 43]。

3.5 不同手术方式的影响

HLHS 患儿社会适应能力较差，选择 Hybrid 术式较选择 Norwood 者 2 岁时的 NDD 风险轻微增加^[46]；对可能进展为 HLHS 的主动脉狭窄胎儿进行主动脉瓣成形术，其适应能力评分低于一般人群，与未进行胎儿手术的 HLHS 患儿相似^[49]；有主动脉阻断史的 CHD 患者 ASD 风险更高^[2]。

3.6 不同 CHD 并发症或合并症的影响

与对照组比较，并发 HF 的非发绀型 CHD 患儿，语言、记忆和学习特定领域评分较低，而并发 HF 的发绀型 CHD 患儿，IQ、语言、记忆和学习特定领域评分均较低，以出生时同时存在发绀和 HF 者最为明显^[50]。术后并发慢性低氧血症者问题处理速度明显下降^[48]，而术后需要进行体外膜肺治疗者，大运动能力较低、问题解决技巧较差和总评分较低^[51]。合并基因缺陷者，更容易发生 IDD^[2]。CHD 早产儿认知障碍和 IDD 发生风险较高，CHD 极低出生体重儿语言发育、认知能力及运动发育评分明显降低^[52]，而进行心脏手术的 CHD 小于胎龄儿 IQ 较非小于胎龄儿更低^[33]。

3.7 其他

母亲患心血管疾病，其子代 ADHD 和 ASD 较多见^[53]；先兆子痫可与 CHD 协同作用，增加患儿 NDD 风险^[54]。家庭社会经济地位较低的 CHD 患儿在精细运动、解决问题能力、适应行为和交流技巧等方面表现较差^[47]。男性 CHD 患儿精神健康问题较女性多见^[35]。

4 CHDNDD 患儿的随访管理

CHD 患儿 NDD 患病率高达 44%，致残率高，其脑结构改变始于宫内，并持续存在；不同情况的 CHD 患儿，其 CHDNDD 临床特点各有不同，需要从胎儿到成年的多学科合作，进行一体化管理及全生命周期健康管理；重视宣教，在患儿病情稳定后，尽快根据 CHDNDD 各临床特点，针对性开展重症监护病房内父母参与式 PEIS，即在患儿

病因解除和病情稳定后，针对其高危因素在不同年龄阶段可能引起而又尚未发生的潜在风险进行有目的的早期干预，以期减少其发生风险，提高干预效果，降低后遗症发生率；并在出院回家后，针对性开展 CHDNDD 家庭监测与医院指导的家庭 PEIS，以及定期回医院随访与筛查，在关键年龄阶段对特定能区进行重点专业评估，针对其可能发生的 CHDNDD 进行有目的的 PEIS 指导及目标导向的强化训练与康复训练，以期更有效地降低 CHDNDD 和 CP 发生率^[7]；利用现有预测工具进行预测，并进行家庭监测，更早发现早期症状，促进家长回医院进行专业的筛查、诊断与干预；结合我国国情，医院指导的家庭 PEIS、个体化家庭回访及基于社区的同伴支持团体的结合式干预，可能是目前 CHDNDD 早期干预的最佳策略^[7]；而掌握小儿生长发育规律，熟悉 CHDNDD 临床特点，是开展家庭 PEIS 的重要基础^[7]。

5 总结与展望

对 CHD 患儿，在医院“早期筛查、早期诊断、早期干预”诊疗策略基础上，进行分级干预，包括早期养育干预、针对不同潜在风险的预防性早期干预，以及目标导向的强化训练与康复训练，实施多学科合作的儿童全生命早期一体化管理，以及从胎儿、新生儿到成人的全生命周期健康管理，有望进一步降低 CHD 患儿后遗症发生率，促进其全面发展和素质提升。

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