

· 论 著 ·

基于微生物-肠-脑轴的维生素 D 改善孤独症症状
效果评价研究☆黄浩宇* 杜晓亮** 王静* 吴金庭* 邹卓* 陈颖娟* 刘芸*[✉]

【摘要】目的 基于微生物-肠-脑轴分析维生素 D 对孤独症(autism spectrum disorder, ASD)患儿症状的改善效果。方法 将 72 例 ASD 患儿随机分为观察组和对照组,每组 36 例,其中对照组脱落 3 例。观察组在常规康复训练基础上补充 1200 IU/d 的维生素 D,对照组仅采用常规康复训练,干预 12 周。干预前后进行儿童孤独症评定量表(childhood autism rating scale, CARS)、儿童孤独症行为量表(autism behavior checklist, ABC)、重复刻板行为检查表-修订版(repetitive behavior scale-revised, RBS-R)评估,近红外脑功能成像检测静息态脑功能连接强度,以及检测血清 25(OH)D₃水平、血清炎症因子水平及肠道菌群,比较两组各指标前后差值以评价临床疗效。结果 干预前后差值比较,观察组 CARS 量表评分(-5.92±1.40 vs. -2.55±1.43)、RBS-R 量表评分(-5.99±1.01 vs. -3.10±1.47)、静息态脑功能连接值(0.19±0.15 vs. 0.10±0.18)、血清 25(OH)D₃水平[(34.89±8.18)ng/mL vs. (0.68±6.73)ng/mL]、血清白介素-6 水平[(-6.60±6.07)pg/mL vs. (-0.74±9.45)pg/mL]、白介素-1β 水平[(-2.56±1.33)pg/mL vs. (-0.04±2.13)pg/mL]、肿瘤坏死因子-α 水平[(-4.09±3.85)pg/mL vs. (0.21±4.05)pg/mL]的干预前后差值优于对照组($P<0.05$)。干预后两组肠道微生物 β 多样性差异有统计学意义($R^2=0.030$, $P=0.040$, Adonis)。LEfSe 结果提示干预后梭菌纲(LDA=4.747, $P=0.003$)、梭菌目(LDA=4.747, $P=0.003$)、梭菌科(LDA=3.476, $P=0.001$)、毛螺菌科(LDA=4.709, $P=0.004$)、气味杆菌科(LDA=3.458, $P=0.027$)、气味杆菌属(LDA=3.458, $P=0.027$)、伯克霍尔德氏菌目(LDA=3.339, $P=0.038$)、厚壁菌门(LDA=4.764, $P=0.003$)、β-变形菌纲(LDA=3.338, $P=0.037$)在观察组富集。结论 补充维生素 D 能调节 ASD 患儿的肠道微生物多样性,显著影响特定肠道微生物丰度,降低机体炎症因子,增加脑功能连接强度,缓解 ASD 临床症状。

【关键词】孤独症谱系障碍 维生素 D 16S rRNA 微生物-肠-脑轴 肠道微生物 炎症因子 脑功能连接

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Evaluation of the effect of vitamin D on improving autism symptoms based on the microbiota-gut-brain axis. HUANG Haoyu, DU Xiaoliang, WANG Jing, WU Jinting, ZOU Zhuo, CHEN Yingjuan, LIU Yun. Department of Rehabilitation, Department of Science, Education and Training, Kunming Children's Hospital (Children's Hospital Affiliated to Kunming Medical University), Kunming 650228, China. Tel: 0871-63309329.

【Abstract】 **Objective** To analyze the symptomatic improvement effects of vitamin D in children with autism spectrum disorder (ASD) based on the microbiota-gut-brain axis. **Methods** Seventy-two children with ASD were randomly divided into an observation group and a control group, with 36 cases in each group. Three cases dropped out in the control group. The observation group received 1200 IU/day of vitamin D supplementation in addition to conventional

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rehabilitation training, while the control group received only conventional rehabilitation training. The intervention lasted for 12 weeks. Assessments were conducted before and after the intervention using the childhood autism rating scale (CARS), autism behavior checklist (ABC), and repetitive behavior scale-revised (RBS-R). Resting-state functional connectivity of the brain was measured using near-infrared functional imaging, and serum levels of 25(OH)D₃, inflammatory cytokines, and gut microbiota were analyzed. The differences in these indicators before and after the intervention were compared between the two groups to evaluate clinical efficacy. **Results** The between-group differences in pre- and post-intervention changes showed that the observation group had significantly greater improvements than the control group in the following measures: CARS scores (-5.92 ± 1.40 vs. -2.55 ± 1.43), RBS-R scores (-5.99 ± 1.01 vs. -3.10 ± 1.47), resting-state brain functional connectivity (0.19 ± 0.15 vs. 0.10 ± 0.18), serum 25(OH)D₃ levels [(34.89 ± 8.18) ng/mL vs. (0.68 ± 6.73) ng/mL], serum interleukin-6 (IL-6) levels [(-6.60 ± 6.07) pg/mL vs. (-0.74 ± 9.45) pg/mL], IL-1 β levels [(-2.56 ± 1.33) pg/mL vs. (-0.04 ± 2.13) pg/mL], and tumor necrosis factor- α (TNF- α) levels [(-4.09 ± 3.85) pg/mL vs. (0.21 ± 4.05) pg/mL] ($P < 0.05$). Post-intervention, significant differences in gut microbial β -diversity were observed between the two groups ($R^2 = 0.030$, $P = 0.040$, Adonis). LEfSe analysis revealed that the observation group exhibited enrichment in Clostridia (LDA=4.747, $P = 0.003$), Clostridiales (LDA=4.747, $P = 0.003$), Clostridiaceae (LDA=3.476, $P = 0.001$), Lachnospiraceae (LDA=4.709, $P = 0.004$), Odoribacteraceae (LDA=3.458, $P = 0.027$), *Odoribacter* (LDA=3.458, $P = 0.027$), Burkholderiales (LDA=3.339, $P = 0.038$), Firmicutes (LDA=4.764, $P = 0.003$), and Betaproteobacteria (LDA=3.338, $P = 0.037$). **Conclusion** Vitamin D supplementation can modulate gut microbial diversity in children with ASD, significantly influence the abundance of specific gut microbiota, reduce systemic inflammatory cytokines, enhance brain functional connectivity, and alleviate clinical symptoms of ASD.

【Keywords】 Autism spectrum disorder Vitamin D 16S rRNA Microbiota-gut-brain axis Gut microbiota Inflammatory factors Brain functional connectivity

孤独症谱系障碍 (autism spectrum disorder, ASD) 是一组复杂的神经发育性障碍。随着微生物-肠-脑轴 (microbiota-gut-brain axis, MGBA) 研究深入, 越来越多证据表明肠道微生物与大脑之间的作用在 ASD 发生和发展中扮演着重要角色^[1-4]。此外, 有研究报道 ASD 儿童的血清 25(OH)D 水平显著低于健康儿童^[5-7], 妊娠期和婴幼儿期维生素 D 缺乏可能是 ASD 的一个危险因素^[8-10]。然而, 维生素 D 治疗 ASD 的效果尚未明确且机制不清。考虑到维生素 D 及其信号通路可影响肠道屏障完整性、肠道固有免疫和适应性免疫以及肠道微生物组成^[11-12], 本研究基于 MGBA 探讨维生素 D 改善 ASD 行为的临床效果, 以期临床寻找出更有效的治疗方案。

1 对象与方法

1.1 研究对象 研究对象来源于昆明市儿童医院康复科 2022 年 1 月至 2023 年 12 月收治的 ASD 儿童。入组标准: ①符合《精神障碍诊断与统计手册第 5

版》(*Diagnostic and Statistical Manual of Mental Disorder*, 5th Edition, DSM-5) 中 ASD 的诊断标准; ②年龄 > 36 个月; ③血清 25(OH)D 水平低于 30 ng/mL。排除标准: ①患有其他严重精神疾病; ②有代谢性疾病、脑器质性疾病及其他严重躯体疾病史; ③近 2 个月内服用过维生素补充剂; ④近 4 周内使用抗生素或益生菌。最终纳入 72 例患儿, 按照随机数字表将 72 例 ASD 患儿分为两组, 每组 36 例。研究过程中对照组 3 例患儿脱落, 最终入选 69 例 ASD 患儿 (观察组 36 例, 对照组 33 例)。受试者入组前由家属签署知情同意书。本研究通过昆明市儿童医院伦理委员会批准 (审批号: 2020-03-132-K0)。

1.2 干预方法 采用单盲设计, 干预前后由同一评估人员进行评估, 评估人员不清楚患者分组情况, 以保证评估数据的客观性。观察组在接受常规康复训练的基础上补充维生素 D [生产厂家: 国药控股星鲨制药 (厦门) 有限公司; 批准文号: 国药准字 H35021450; 药品规格: 400 IU/粒], 根据美国内分泌协会指南建议^[13]进行 1200 IU/d 的维生素 D 补充。

对照组仅接受常规康复训练,两组常规康复训练一致。共干预12周。

1.3 评价指标

1.3.1 ASD行为评分 使用儿童孤独症评定量表(childhood autism rating scale, CARS)、儿童孤独症行为量表(autism behavior checklist, ABC)、重复刻板行为检查表-修订版(repetitive behavior scale-revised, RBS-R)评估患儿的ASD行为。

1.3.2 静息态脑功能连接强度分析 使用近红外脑功能成像系统(NirScan-6000C, 丹阳慧创医疗设备有限公司)测量静息态下额颞叶氧合血红蛋白浓度变化。数据采集时要求患儿由监护人抱住,静坐休息,采集5 min数据。选取双侧背外侧前额叶皮质、双侧运动前皮质及双侧颞叶皮质作为感兴趣区。使用NirSpark软件进行数据处理和分析,采用Pearson相关法计算各通道、脑区时间序列上氧合血红蛋白的相关系数 r 值并进行Fisher- Z 转换,转换后的数值为对应通道的静息态功能连接强度值(resting-state functional connectivity, rsFC)。

1.3.3 血清25(OH) D_3 、炎症因子检测 干预前及干预12周后采集空腹静脉血,利用高效液相色谱技术与罗氏全自动生化分析仪检测血清25(OH) D_3 水平,采用酶联免疫吸附法测定血清白细胞介素-6(interleukin-6, IL-6)、白细胞介素-1 β (interleukin-1 β , IL-1 β)、肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)水平。

1.3.4 基于16S rRNA测序的肠道微生物组学分析 干预前及干预12周后分别采集患儿粪便样本,采集后迅速置于-80℃冻存,超低温运至实验室。使用Zymo Research BIOMICS DNA Microprep Kit试剂盒提取DNA,用Tecan F200进行纯度检验;对16S rRNA V4区域(扩增引物515F:5'-GTGYCAGCMGCCGCGGTAA-3'和806R:5'-GGACTACHVGGGTWTCTAAT-3')进行PCR扩增;提取扩增子并使用Zymoclean凝胶回收试剂盒进行回收,使用Qubit®2.0 Fluorometer(Thermo Scientific)荧光定量;使用Illumina(NEB#E7645L)构建文库;采用Illumina Nova-

Seq6000平台进行高通量双端测序。使用Kraken2软件和R语言对测序数据进行处理和分析。

1.4 统计学方法 数据采用SPSS 25.0进行统计学分析。运用 χ^2 检验和独立样本 t 检验对人口学资料进行组间比较;采用独立样本 t 检验对比两组CARS评分、ABC评分、RBS-R评分、rsFC值、血清25(OH) D_3 水平和炎症因子水平的干预前后差值。采用QIIME 2软件进行 α 和 β 多样性分析。 α 多样性包括Chao1和Shannon指数。使用基于Bray-Curtis距离的主坐标分析(principal co-ordinates analysis, PCoA)比较样本的 β 多样性,组间差异用Adonis检验。使用线性判别分析(linear discriminant analysis effect size, LEfSe)筛选差异菌群,LEfSe是基于Wilcoxon秩和检验分析组间差异菌属,并计算出不同菌属的效应值LDA大小,筛选条件为LDA ≥ 2.0 且 $P < 0.05$ 。检验水准 $\alpha = 0.05$,双侧检验。

2 结果

2.1 人口学资料 共纳入69例ASD患儿,其中观察组36例,对照组33例。两组性别($\chi^2 = 0.169$, $P = 0.681$)、月龄($t = 0.141$, $P = 0.888$)、病程($t = 0.771$, $P = 0.444$)差异无统计学意义($P > 0.05$)。见表1。

Tab.1 Demographic characteristics of two groups

表1 两组患儿人口学特征

组别	n	性别		月龄(月)	病程(月)
		男	女		
观察组	36	31	5	49.85 $\pm$ 12.75	12.11 $\pm$ 5.12
对照组	33	28	5	50.27 $\pm$ 11.92	13.04 $\pm$ 4.88

2.2 干预前后两组患儿ASD行为评分 干预前,两组患儿各项量表评分差异无统计学意义($P > 0.05$)。干预12周后,观察组CARS量表($t = 9.886$, $P < 0.001$)、RBS-R量表($t = 9.435$, $P < 0.001$)前后得分的差值优于对照组,而ABC量表评分差值的组间差异无统计学意义($P > 0.05$)。见表2。

2.3 干预前后两组患儿静息态脑功能连接强度 干预前,两组患儿额颞叶rsFC值组间差异无统计学意义($P > 0.05$)。干预12周后,观察组rsFC前后差值优于对照组($t = 2.263$, $P = 0.027$)。见表2。

Tab.2 ASD behavioral scores, rsFC of the frontal and temporal lobes and their differences before and after intervention of two groups
表2 两组患儿干预前后ASD行为评分、额颞叶rsFC及其差值

组别	n	CARS量表评分(分)			ABC量表评分(分)			RBS-R量表评分(分)			rsFC		
		干预前	干预后	差值	干预前	干预后	差值	干预前	干预后	差值	干预前	干预后	差值
观察组	36	37.63±3.01	31.71±2.81	-5.92±1.40 ¹⁾	67.35±11.33	56.10±2.55	-11.25±3.92	19.65±2.79	13.66±1.04	-5.99±1.01 ¹⁾	0.11±0.11	0.30±0.10	0.19±0.15 ¹⁾
对照组	33	36.15±3.55	33.6±1.89	-2.55±1.43	68.07±10.14	57.53±3.43	-10.54±3.79	18.72±3.31	15.62±2.53	-3.10±1.47	0.10±0.11	0.20±0.14	0.10±0.18

注:CARS,儿童孤独症评定量表;ABC,儿童孤独症行为量表;RBS-R,重复刻板行为检查表-修订版;rsFC,静息态功能连接强度值。1)与对照组比较,经独立样本t检验,P<0.01。

2.4 干预前后两组患儿血清 25(OH)D₃和炎症因子水平 干预前,两组患儿血清 25(OH)D₃、IL-6、IL-1β、TNF-α水平差异无统计学意义(P>0.05)。干预12周后,观察组血清 25(OH)D₃(t=18.870, P<0.001)、IL-6(t=3.034, P<0.001)、IL-1β(t=5.831, P<0.001)、TNF-α(t=4.521, P<0.001)水平前后差值优于对照组。见表3。

2.5 肠道微生物多样性分析 肠道微生物α多样性分析提示,干预前观察组和对照组的Chao1指数(t=0.433, P=0.667)和Shannon指数(t=0.272, P=0.786)差异无统计学意义,干预后两组Chao1指数(t=0.175, P=0.863)和Shannon指数(t=0.578, P=0.569)差异也无统计学意义。肠道菌群的β多样性PCoA分析提示,干预前两组患儿Bray_Curtis距离差异无统计学意义(R²=0.019, P=0.291, Adonis),干预后Bray_Curtis距离差异有统计学意义(R²=0.030, P=0.040, Adonis)。见图1。

2.6 肠道微生物差异分析 门水平,优势菌为厚壁菌门、拟杆菌门、变形菌门、梭杆菌门和疣微菌门,干预后观察组变形菌门相对丰度变化差异有统计学意义(t=2.585, P=0.013),见图2。属水平,优势菌为拟杆菌属、粪杆菌属、大肠杆菌属、布劳特氏菌属,见图3。

LEfSe分析示,干预后观察组富集的有梭菌纲

(Clostridia)(LDA=4.747, P=0.003)、梭菌目(Clostridiales)(LDA=4.747, P=0.003)、梭菌科(Clostridiaceae)(LDA=3.476, P=0.001)、毛螺菌科(Lachnospiraceae)(LDA=4.709, P=0.004)、气味杆菌科(Odoribacteraceae)(LDA=3.458, P=0.027)、气味杆菌属(Odoribacter)(LDA=3.458, P=0.027)、伯克霍尔德氏菌目(Burkholderiales)(LDA=3.339, P=0.038)、厚壁菌门(Firmicutes)(LDA=4.764, P=0.003)、β-变形菌纲(Betaproteobacteria)(LDA=3.338, P=0.037);对照组富集的有普罗威登斯菌属(Providencia)(LDA=4.458, P=0.001)、摩根菌科(Morgenllaceae)(LDA=4.459, P=0.001)。见图4。

3 讨论

维生素D缺乏被认为是ASD的危险因素之一,ASD症状严重程度与血清维生素D浓度呈负相关^[14]。在本研究中,观察组干预前后的CARS和RBS-R量表评分差值高于对照组,这表明常规康复联合大剂量维生素D(1200 IU/d)干预能更有效地改善维生素D缺乏ASD患儿的核心症状,这一结果与JAVADFAR等^[15]、MAZAHERY等^[16]、冯俊燕等^[17]的研究结果一致。两组患儿干预前后ABC量表评分差值在本研究中没有显著差异,在感觉、交往、躯体运动、语言和生活自理分因子中均无差异还是部分有差异还待进一步分析。

Tab.3 Serum 25(OH)D₃, inflammatory factor levels and their differences before and after intervention of two groups
表3 两组患儿干预前后血清 25(OH)D₃、炎症因子水平及其差值

组别	n	25(OH)D ₃ (ng/mL)			IL-6(pg/mL)			IL-1β(pg/mL)			TNF-α(pg/mL)		
		干预前	干预后	差值	干预前	干预后	差值	干预前	干预后	差值	干预前	干预后	差值
观察组	36	14.62±6.41	49.51±9.48	34.89±8.18 ¹⁾	12.91±8.14	6.31±3.52	-6.60±6.07 ¹⁾	8.09±1.17	5.53±1.62	-2.56±1.33 ¹⁾	12.15±4.45	8.06±3.14	-4.09±3.85 ¹⁾
对照组	33	14.21±7.73	14.89±5.62	0.68±6.73	13.11±7.38	12.37±10.73	-0.74±9.45	8.11±1.03	8.07±2.42	-0.04±2.13	11.87±4.44	12.08±3.75	0.21±4.05

注:IL-6,白细胞介素-6;IL-1,白细胞介素-1β;TNF-α,肿瘤坏死因子-α。1)与对照组比较,经独立样本t检验,P<0.01。

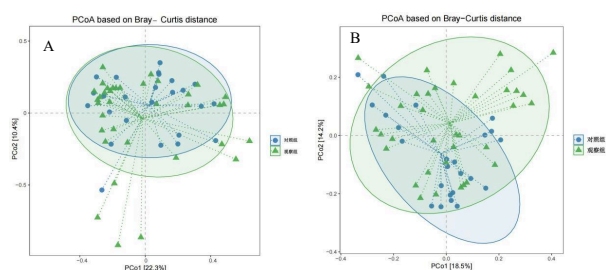


Fig.1 Comparison of gut microbiota beta diversity in the two groups of children before and after intervention

图1 两组患儿干预前后肠道微生物 beta 多样性比较

A. 干预前; B. 干预后。

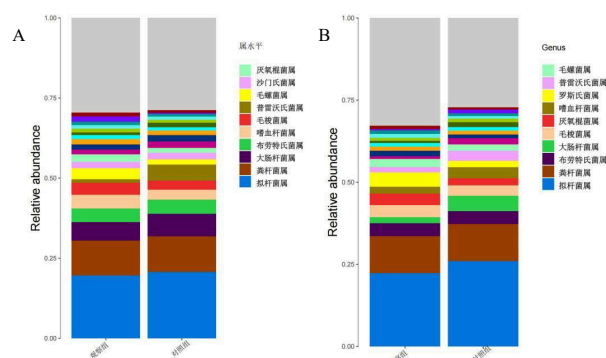


Fig.3 Barplot of the dominant flora at the genus level in the two groups of children before and after the intervention

图3 两组患儿干预前后属水平优势菌群的物种累积柱状图

A. 干预前; B. 干预后。

在本研究中,观察组干预前后的rsFC强度差值显著高于对照组,此结果与ZHAO等^[18]使用功能磁共振研究维生素D对重性抑郁障碍患者大脑结构和功能连接的结果相一致。多项证据^[19-21]表明维生素D在大脑发育、突触可塑性、神经保护和多巴胺能系统中具有生理学作用,并参与特定神经回路的传输与连接。此外,维生素D可通过调节肠道微生物群落的组成和功能,改善肠道屏障功能,减少炎症反应,促进有益菌产生神经活性代谢产物^[22],这些代谢产物通过MGBA传递到大脑,进一步调节神经递质平衡、减轻神经炎症、促进神经保护,最终提高大脑的功能连接强度^[23]。

免疫因素可能在ASD的病因学中发挥重要作用,先天免疫系统异常可能是ASD的一个主要特征^[24]。近年来,IL-6和TNF- α 在ASD中的影响已在ASD的病理生理学中得到证实。在本研究中,干

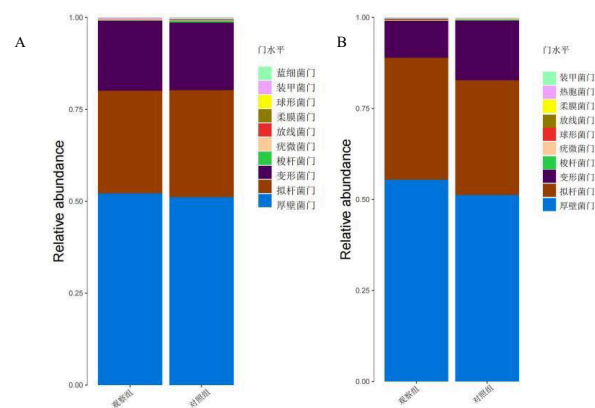


Fig.2 Barplot of the dominant flora at the phylum level in the two groups of children before and after the intervention

图2 两组患儿干预前后门水平优势菌群的物种累积柱状图

A. 干预前; B. 干预后。

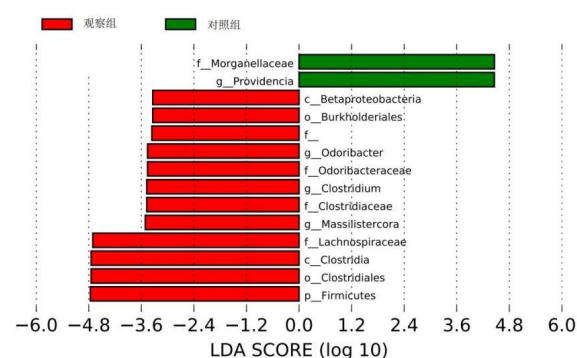


Fig.4 Column plot of linear discriminant analysis (LDA) scores calculated according to differential enriched genera between groups after the intervention

图4 两组患儿干预后组间差异菌属线性判别分析(LDA)得分列线图

预后观察组的IL-6、IL-1 β 、TNF- α 水平降低,这一结果与JAVADFAR等^[15]的研究结果一致。维生素D可通过调节炎症细胞因子的产生来减轻炎症,高剂量的维生素D可以抑制辅助性T细胞1型介导的免疫反应,从而抑制多种促炎细胞因子的产生,包括IL-6、IL-1 β 和TNF- α ,同时促进抗炎细胞因子的产生^[25]。

作为MGBA中的核心,肠道微生物是影响大脑发育和功能的关键因素^[26]。本研究详细分析维生素D对ASD患儿肠道微生物的影响,与TABSSUM等^[27]、SOLTYS等^[28]的研究结果一致,本研究中干预后观察组ASD患儿变形菌门和大肠杆菌属相对丰

度降低。变形菌门增多是肠道微生物紊乱的标志,变形菌门可引起肠道黏膜炎症反应,进一步影响上丘脑-垂体-肾上腺轴,进而引起心理行为改变^[29-30]。本研究中LEfSe分析发现,干预后观察组的毛螺菌科(Lachnospiraceae)、气味杆菌属(*Odoribacter*)、 β -变形菌纲(Betaproteobacteria)丰度上调,这与HE等^[31]、XIANG等^[32]的研究结果一致。毛螺菌科能够产生短链脂肪酸,如丙酮和丁酸,对人体肠道健康和能量供应起着重要作用^[33],而丁酸具有调节肠道屏障功能、改善ASD行为的重要作用^[34]。因此,补充维生素D对ASD患儿肠道微生物的作用值得进一步研究。

本研究结果提示补充维生素D能改善ASD临床症状,并对ASD患儿肠道微生物、外周炎症及脑功能连接有积极影响。但本研究仍存在一些不足:第一,样本量较小;第二,未进行神经递质、肠道屏障功能和微生物代谢物的检测,未能覆盖MGBA所有范畴。未来需开展多中心研究以深入分析维生素D基于MGBA在ASD中发挥的作用,为开发更为精准和靶向的ASD治疗策略提供科学依据。

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