

## · 论著 ·

## 特发性身材矮小患儿肠道菌群改变及其与体格发育的关系分析

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**【摘要】目的** 观察特发性身材矮小(ISS)患儿肠道菌群变化,并分析其与患儿体格发育的关系。**方法** 选取本院2020年5月至2022年5月收治的106例ISS患儿设为ISS组,另同期选取106例在本院行健康体检的正常儿童作为对照组,检测两组体格发育指标[包括身高、体重、身体质量指数(BMI)、骨龄],并收集粪便样本检测肠道菌群,另采用Pearson法分析ISS患儿肠道菌群与体格发育指标的相关性。**结果** ISS组身高、体重、BMI、骨龄均低于对照组( $P<0.05$ );ISS组与对照组肠道菌群检出率无显著差异( $P>0.05$ );ISS组酵母菌、肠球菌、产气荚膜梭菌水平比较无明显差异( $P>0.05$ ),ISS组大肠杆菌水平高于对照组,乳酸杆菌、双歧杆菌、拟杆菌水平低于对照组( $P<0.05$ );ISS患儿乳酸杆菌、双歧杆菌水平与身高、体重、BMI、骨龄呈正相关( $P<0.05$ ),拟杆菌水平与身高、体重、BMI呈正相关( $P<0.05$ )。**结论** ISS患儿乳酸杆菌、双歧杆菌、拟杆菌等厌氧菌水平明显下降,肠杆菌、乳酸杆菌、双歧杆菌、拟杆菌水平与体格发育指标具有相关性,可能是ISS发病的原因之一。

**【关键词】** 儿童;特发性身材矮小;肠道菌群;体格发育

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## Analysis of the Relationship between Intestinal Microflora and Physical Development in Children with Idiopathic Short Stature

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**Abstract: Objective** To observe the changes of intestinal flora in children with idiopathic short stature (ISS) and analyze the relationship between intestinal flora and physical development of children. **Methods** 106 children with ISS admitted to our hospital from May 2020 to May 2022 were selected as the ISS group, and 106 normal children who underwent physical examination in our hospital were selected as the control group at the same time. The two groups of physical development indicators [including height, weight, body mass index (BMI), bone age] were tested, and stool samples were collected to detect intestinal flora. Pearson method was used to analyze the correlation between intestinal flora and physical development indicators in children with ISS. **Results** The height, weight, BMI and bone age of ISS group were lower than those of control group ( $P<0.05$ ). There was no significant difference in the detection rate of intestinal flora between ISS group and control group ( $P>0.05$ ). There was no significant difference in the levels of Yeast, Enterococcus and Clostridium perfringens between the ISS group and the control group ( $P>0.05$ ). The levels of Escherichia coli in the ISS group were higher than those in the control group, while the levels of Lactobacillus, Bifidobacterium and Bacteroides were lower than those in the control group ( $P<0.05$ ). The levels of Lactobacillus and Bifidobacterium were positively correlated with height, weight, BMI and bone age ( $P<0.05$ ), and the level of Bacteroides was positively correlated with height, weight and BMI ( $P<0.05$ ). **Conclusion** The levels of Lactobacillus, Bifidobacterium, Bacteroides and other anaerobic bacteria in children with ISS decreased significantly. The levels of Enterobacillus, Lactobacillus, Bifidobacterium and Bacteroides are correlated with physical development indicators, which may be one of the causes of ISS.

**Keywords:** Children; Idiopathic Short Stature; Intestinal Flora; Physical Development

特发性身材矮小(ISS)是指不伴有潜在病理状态且生长激素水平正常的身材矮小,在身材矮小儿童中占60%~80%,是导致儿童期身材矮小的常见原因<sup>[1]</sup>。ISS病因未明,目前多认为与遗传变异、环境、营养等有关<sup>[2]</sup>,现临床尚无特效治疗方法,多采用生长激素治疗,虽能短期改善生长发育,但仍有部分患儿疗效欠佳,且生长激素治疗存在一定的副作用和风险<sup>[3]</sup>。因此,积极探讨ISS的发病机制对指导临床制定合理的治疗方案意义重大。近年来越来越多研究报道肠道菌群在疾病发生发展中的作用,不少学者提出肠道菌群与生长发育存在关联,Ronan V等<sup>[4]</sup>报道肠道微生物组从出生到成年不断变化,是影响儿童发育的重要系统;Barratt MJ等<sup>[5]</sup>发现儿童消瘦、发育迟缓可能受产后肠道微生物群发育影响,但在ISS患儿中肠道菌群改变是否与体格发育有关尚缺乏研究报道。鉴于此,本研究对比106例ISS患儿和106例正常儿童肠道菌群及体格发育情况,分析肠道菌群与ISS患儿体格发育的关系,以期为进一步了解ISS发病机制及制定治疗方案提供参考。

### 1 资料与方法

#### 1.1 一般资料

选取本院2020年5月至2022年5月收治的106例ISS

患儿设为ISS组,另同期选取106例在本院行健康体检的正常儿童作为对照组。

纳入标准:年龄4~12岁;均为汉族;出生时身高、体重均正常;ISS组患儿符合ISS相关诊断标准<sup>[6]</sup>,身高低于同种族、同年龄、同性别正常儿童均值的2个标准差;对照组儿童身体健康,生长发育正常,无重大疾病史;所有入组儿童监护人均知情并自愿参与本研究。排除标准:合并代谢性疾病;合并畸形、骨骼发育障碍及心肝肾等器质性疾病;存在染色体异常;合并精神、心理疾病;生长激素缺乏;入组前有促生长治疗史;近3个月有益生菌、抗生素等治疗史。ISS组男61例、女45例,年龄4~12(7.55±1.16)岁;对照组男61例,女45例,年龄4~12(7.48±1.34)岁,两组性别、年龄比较差异无统计学意义( $P>0.05$ )。

#### 1.2 方法

1.2.1 体格发育指标检测 采用身高体重秤于上午8~10点测量,受试儿童均空腹、赤足免冠、着单薄衣物,正位站立于双脚标识处,保持两眼平视前方、双手自然下垂、两腿伸直,记录受试儿童身高、体重和身体质量指数(BMI)数值。采用德国西门子X射线

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机拍摄受试儿童左手腕关节正位片, 受试儿童左手五指自然张开放在暗盒中心, 手掌紧贴平面, 中指、第3掌骨、前臂保持在同一轴线上, X片需包括手掌指骨、腕部、尺骨与桡骨远端4cm, 由医院同一经验丰富的放射科医生遵循《中国儿童骨龄评分法》<sup>[7]</sup>图谱进行骨龄评分。

1.2.2 肠道菌群检测 收集受试儿童自然排出的未经污染的中段新鲜粪便5g置于粪便采集器中, 分成两份于半小时内放入-80℃冰箱保存。采用光冈氏肠内细菌群分析法, 取1g粪便样本用无菌稀释液稀释, 依次按10倍稀释到10<sup>-8</sup>, 分别取50μl不同稀释度液涂抹在培养基上进行培养, 对菌群进行定性定量测定。选取具有代表性的肠道菌群, 需氧菌(酵母菌、肠球菌、肠杆菌)37℃培养48~72h, 厌氧菌(乳酸杆菌、双歧杆菌、拟杆菌、产气荚膜梭菌)37℃厌氧培养48h, 统计各菌属检出率, 计算每克粪便样本中的菌落含量, 取3个平板上菌落平均值, 以log CFU/g换算结果, 检测下限为2×10<sup>2</sup> log CFU/g湿便。

1.2.3 质量控制 所有医护人员均经专业培训, 所有受试儿童均采用同一身高体重秤和X射线机, 仪器均经校准; 研究数据均双人核对录入。

1.3 统计学方法 研究数据采用SPSS 26.0软件进行处理, 计量资料以均数±标准差( $\bar{x} \pm s$ )描述, 两组间差异采用独立样本t检验; 计数资料以例数/百分率(n/%)描述, 两组间差异采用检验。采用Pearson法分析ISS患儿肠道菌群与体格发育指标的相关性。P<0.05为差异有统计学意义。

## 2 结果

2.1 ISS组与对照组儿童体格发育指标比较 ISS组身高、体重、BMI、骨龄均低于对照组(P<0.05), 见表1。

2.2 ISS组与对照组肠道菌群检出率 ISS组与对照组酵母菌、肠球菌、大肠杆菌、乳酸杆菌、双歧杆菌、拟杆菌、真杆菌、产气荚膜梭菌检出情况见表2, 组间比较无显著差异(P>0.05)。

2.3 ISS组与对照组肠道菌群水平比较 ISS组酵母菌、肠球菌、产气荚膜梭菌水平比较无明显差异(P>0.05), ISS组大肠杆菌水平高于对照组, 乳酸杆菌、双歧杆菌、拟杆菌水平低于对照组(P<0.05), 见表3。

2.4 ISS患儿肠道菌群水平与体格发育指标的相关性分析 Pearson分析结果显示, ISS患儿酵母菌、肠球菌、大肠杆菌、产气荚膜梭菌水平与体格发育指标无相关性(P>0.05), 乳酸杆菌、双歧杆菌水平与身高、体重、BMI、骨龄呈正相关(P<0.05), 拟杆菌水平与身高、体重、BMI呈正相关(P<0.05), 见表4。

表1 ISS组与对照组儿童体格发育指标比较

组别	n	身高(cm)	体重(kg)	BMI(kg/m <sup>2</sup> )	骨龄(岁)
ISS组	106	115.10±12.74	18.86±1.57	14.32±1.04	6.24±1.25
对照组	106	129.44±14.09	24.72±2.93	14.85±1.98	7.36±1.41
t值		7.772	18.150	2.440	6.120
P值		<0.001	<0.001	0.016	<0.001

表2 ISS组与对照组肠道菌群检出率比较[n(%)]

组别	n	酵母菌	肠球菌	大肠杆菌	乳酸杆菌	双歧杆菌	拟杆菌	产气荚膜梭菌
ISS组	106	47(44.34)	106(100.00)	106(100.00)	104(98.11)	106(100.00)	106(100.00)	49(46.23)
对照组	106	55(51.89)	106(100.00)	106(100.00)	106(100.00)	106(100.00)	106(100.00)	41(38.68)
$\chi^2$ 值		1.209	—	—	2.019	—	—	46.23
P值		0.271	—	—	0.155	—	—	38.68

表3 ISS组与对照组肠道菌群水平比较(log CFU/g)

组别	n	酵母菌	肠球菌	大肠杆菌	乳酸杆菌	双歧杆菌	拟杆菌	产气荚膜梭菌
ISS组	106	4.72±0.82	6.32±1.15	7.42±0.66	6.69±0.70	6.14±0.57	8.29±0.78	6.04±0.69
对照组	106	4.87±0.65	6.51±1.04	6.83±0.74	7.98±0.84	8.65±0.53	9.23±1.06	5.88±0.62
t值		1.476	1.262	6.126	12.146	33.202	7.354	1.776
P值		0.141	0.208	<0.001	<0.001	<0.001	<0.001	0.077

表4 ISS患儿肠道菌群水平与体格发育指标的相关性分析

肠道菌群	身高		体重		BMI		骨龄	
	r	P	r	P	r	P	r	P
酵母菌	0.105	0.341	0.212	0.359	0.279	0.485	0.117	0.220
肠球菌	0.139	0.232	0.170	0.464	0.016	0.542	0.184	0.562
大肠杆菌	-0.194	0.165	-0.208	0.364	-0.172	0.668	-0.138	0.256
乳酸杆菌	0.440	0.006	0.316	0.020	0.342	0.024	0.254	0.035
双歧杆菌	0.535	0.004	0.454	0.023	0.508	0.007	0.373	0.016
拟杆菌	0.317	0.011	0.386	0.020	0.302	0.035	0.163	0.094
产气荚膜梭菌	-0.168	0.114	-0.209	0.083	-0.197	0.433	-0.215	0.247

## 3 讨论

身高、体重是反映儿童体格发育最方便、最直观、最常用的指标, 骨龄是反映儿童体格发育的生物年龄, 能够更为真实地评估生长发育水平。本研究中ISS患儿身高、体重、BMI、骨龄均低于正常儿童, 与既往报道一致<sup>[8-9]</sup>, 均证实ISS患儿普遍存在体格发育迟缓。但由于ISS病因尚不明确, 探讨其发病机制以指导干预一直是临床研究的热点。

肠道中蕴藏着大量的菌群, 它们与宿主形成共生关系, 在正常生长发育中发挥重要作用。既往研究发现家蚕肠道微生态受损会影响肠道内相关消化酶的活性、物质转运、消化吸收, 进而影响生长发育<sup>[10]</sup>; 另有研究发现肠道微生物群可介导动物骨骼肌生长发育, 通过将粪便微生物群移植到无菌仔猪中能够促进生长发育<sup>[11]</sup>, 以上研究均证实肠道菌群参与宿主的生长发育过程。本研

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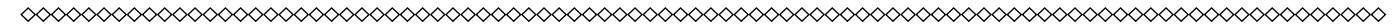
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究采用光冈氏肠内细菌群分析法检测ISS患儿和正常儿童的肠道菌群,发现两组酵母菌、肠球菌、大肠杆菌、乳酸杆菌、双歧杆菌、拟杆菌、真杆菌、产气荚膜梭菌检出率虽无明显差异,但ISS组大肠杆菌水平高于对照组,乳酸杆菌、双歧杆菌、拟杆菌水平低于对照组,提示ISS患儿肠道菌群存在失调现象,尤其是乳酸杆菌、双歧杆菌、拟杆菌等厌氧菌水平明显下降。

为进一步探讨ISS患儿肠道菌群变化与其临床表现的关系,本研究对ISS患儿肠道菌群属水平和体格发育指标进行相关性分析,结果显示乳酸杆菌、双歧杆菌水平与身高、体重、BMI、骨龄呈正相关,拟杆菌水平与身高、体重、BMI呈正相关,提示肠道菌群变化与ISS体格发育存在关联,部分菌群的增加或减少可能参与ISS发病的过程。乳酸杆菌、双歧杆菌是肠道含量较高的有益菌群,能够与有害菌群竞争附着位点和营养物质,抑制有害菌的繁殖,在代谢方面能够促进肠道消化酶的分泌,加快营养物质和微量元素的吸收,帮助合成维生素。既往相关研究报道,乳酸杆菌不仅可以促进肠道菌群的发育和菌落结构平衡,同时能够为宿主提供部分维生素和必需氨基酸,提高宿主营养代谢,促进生长<sup>[12-13]</sup>;双歧杆菌能够提高宿主营养吸收率和生长性能<sup>[14]</sup>。拟杆菌参与肠道碳水化合物发酵、胆汁酸和类固醇生物转化和含氮物质等代谢活动, Li D等<sup>[15]</sup>报道普通拟杆菌、均匀拟杆菌、卵形拟杆菌均与儿童营养代谢指标相关,拟杆菌参与肠道碳水化合物发酵、胆汁酸和类固醇生物转化和含氮物质等代谢活动,据此推测拟杆菌可能通过调节肠道营养物质代谢影响宿主生长发育。

综上所述,ISS患儿相比正常儿童肠道菌群存在失调现象,尤其是乳酸杆菌、双歧杆菌、拟杆菌等厌氧菌水平明显下降,肠杆菌、乳酸杆菌、双歧杆菌、拟杆菌水平与体格发育指标具有相关性,提示肠道菌群变化与ISS发病存在联系,调节肠道菌群有望成为临床治疗ISS的新方向。但本研究仍存在不足,各种肠道菌群参与ISS发病的具体机制尚未完全明确,后续仍需深入研究,其次如何根据本研究结果对ISS患儿进行肠道菌群干预及干预效果也需进一步探讨。

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