doi: 10.13241/j.cnki.pmb.2021.07.034

儿童运动发育迟缓与血碱性磷酸酶、血 25- 羟维生素 D3 表达水平的相关性 *

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摘要 目的:探讨儿童运动发育迟缓与血碱性磷酸酶(Alkaline phosphatase,ALP)、血 25- 羟维生素 D3[25(OH)D3]表达水平的相关性。**方法:**2016 年 10 月到 2018 年 6 月选择在本院儿保科门诊就诊 500 例(6~12 月龄)的儿童作为研究对象,诊断儿童发育迟缓的发生率,检测发育迟缓患儿血清 ALP 与 25(OH)D3 水平,Gesell 测评评定小儿的运动发育状况,所有患儿每天均给予了维生素 D3 400 IU,对于发育迟缓患儿每天给予维生素 D 800 IU~1200 IU 补充,治疗 3 个月,再做 Gesell 测评评估其运动发育水平,对比治疗后运动发育情况,并分析影响儿童运动发育的相关因素。**结果:**在 500 例小儿中,判断为运动发育迟缓 120 例(迟缓组),占比24.0 %。两组小儿的性别、胎龄、分娩方式、出生体重、头围、身长等对比差异无统计学意义(P>0.05)。迟缓组的血清 ALP 水平高于非迟缓组(P<0.05),25(OH)D3 水平低于非迟缓组(P<0.05)。迟缓组的大动作、精细运动、适应性行为、语言、个人社交评分都低于非迟缓组(P<0.05),迟缓组治疗后,大动作、精细运动、适应性行为、语言、个人社交评分均显著升高(P<0.05)。在 120 例发育迟缓中,Pearson 分析显示 ALP、25(OH)D3 与小儿运动迟缓发育具有相关性(P<0.05);二分类多因素条件 Logistic 分析结果显示 ALP、25(OH)D3 都影响儿童运动发育迟缓的主要因素(P<0.05)。**结论:**儿童运动发育迟缓与血清 ALP、25(OH)D3 水平存在相关性,两者的联合检测可为儿童发育迟缓的早期诊断提供实验依据,经过维生素 D 治疗后,能显著的改善其患儿的运动发育,有很好的应用价值。

关键词:儿童;运动发育迟缓;碱性磷酸酶;25- 羟维生素 D3;相关性

中图分类号:R723;Q565;Q55 **文献标识码:**A **文章编号:**1673-6273(2021)07-1356-04

Correlation between Children's Motor Development Delay and Expression of Blood Alkaline Phosphatase and Blood 25-hydroxyvitamin D3*

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ABSTRACT Objective: To explore the correlation between children's motor developmental delay and the expression of blood alkaline phosphatase (ALP) and blood 25-hydroxyvitamin D3[25(OH)D3]. **Methods:** A total of 500 children from 6 - 12 months of age, who went to the pediatric health care department of Northwest Women and Children's Hospital for seeking medical advice from October 2016 to June 2018, were chosen as research subjects. All the children were given 400 IU of vitamin D3 every day, and 800 IU~1200 IU of vitamin D was given to children with developmental delay every day for 3 months. The Gesell test was performed to evaluate their motor development level, and the motor development after treatment was compared. The related factors that affect developmental delay were analyzed. **Result:** Among 500 children, 120 cases were judged to be motor development retardation (delayed group), accounting for 24.0%. There were no significant differences in gender, gestational age, delivery method, birth weight, head circumference, and length between the two groups of children (P>0.05). The serum ALP level of the retarded group was higher than that of the non-retardant group (P<0.05), and the 25(OH)D3 level was lower than that of the non-retarded group (P<0.05). After treatment, the major motor, fine motor, adaptive behavior, language, and personal social scores of the retarded group Both were significantly increased (P<0.05). Among 120 cases of developmental delay, Pearson analysis showed that ALP and 25 (OH)D3 were correlated with children's motor retardation development (P<0.05); the results of two-category multivariate conditional Logistic analysis showed that both ALP and 25(OH)D3 were the main factors of affecting children's motor retardation development (P<0.05). **Conclusions:** There is correlation between children's motor development delay and serum ALP and 25 (OH)D3 levels. The combined detection of the two can provide experimental evidence for the early diagnosis of children's developmental delay. After vitamin D treatment, the motor development of children can be significantly improved, with better application value.

Key words: Children; Motor developmental delay; Alkaline phosphatase; 25-hydroxyvitamin D3; Correlation

Chinese Library Classification(CLC): R723; Q565; Q55 Document code: A

* 基金项目:陕西省卫生健康委基金项目(2018E014)

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(收稿日期:2020-09-05 接受日期:2020-09-28)

Article ID:1673-6273(2021)07-1356-04

前言

发育迟缓是我国小儿常见病,特别是运动发育迟缓比较常见[1]。该病不仅可使小儿骨质软化,骨骼畸形,同时引起造血、免疫、神经、肌肉等组织器官功能异常,使得小儿对肺炎、贫血、呼吸道感染等易感,从而严重影响小儿、家庭与社区的身心健康[2-4]。基础研究表明运动发育迟缓会导致髓鞘合成受阻、脑细胞数目减少和脑容积减少，从而影响小儿的智力与视听发育[5,6]。碱性磷酸酶(Alkaline phosphatase,ALP)检测是早期诊断发育迟缓的方法，它可以在患儿无明显症状时就检出该病[7]。ALP 也是成骨细胞成熟的标志,与骨组织钙化密切相关。但是 ALP 活性易受肝胆疾病的影响,具有比较大的波动性[8,9]。维生素 D 是一种脂溶性维生素,具有调节钙磷代谢与免疫、调控细胞生长分化等作用；维生素 D 的高表达可以促使 B 细胞合成 IgE,拮抗 Th2 细胞反应,抑制角膜炎发病[10,11]。小儿维生素 D 缺乏与骨代谢异常可影响其生长发育，动态监测血清 25 羟 - 维生素 D[25(OH)D3]水平可以指导维生素 D 缺乏的治疗方案[12]。本文具体探讨了儿童运动发育迟缓与血碱性磷酸酶、血 25(OH)D3 表达水平的相关性,以明确儿童运动发育迟缓发生的机制。现总结报道如下。

1 资料与方法

1.1 研究对象

2016 年 10 月到 2018 年 6 月选择在本院儿保科门诊就诊 500 例(6~12 月龄)的儿童作为研究对象,纳入标准:小儿表现为易激惹、睡眠不宁、多汗、夜惊、爱哭闹等症状;小儿家长知情同意本研究;医院伦理委员会批准了此次研究;临床资料完整。排除标准:胎龄 <32 周的早产儿;存在已知的遗传性综合征;正在患病和曾患过神经系统等其他严重疾病的患儿;三级亲属在内有先天性运动功能障碍的小儿。

1.2 血清 ALP 与 25(OH)D3 水平检测

采集所有小儿的末梢血 1~2 mL，置于试管中静止 30 min 后,2000 rpm 离心 20 min,取上层血清,保存 4℃冰箱。采用全自动生化分析仪检测血清 ALP 含量，采用酶联免疫吸附试验检测血清 25(OH)D3 水平。

正常小儿 ALP 活性≤ 200 U/L,25(OH)D3≥ 25 nmol/L。

1.3 运动发育能力评定

采用 Gesell 发育量表评分系统检查运动发育能力,检查内容包括大动作、精细运动、适应性行为、语言、个人社交 5 大领域对患儿的运动功能进行评价,发育商(DQ)<75 分为智力低下,75~85 分为边缘智力水平,>85 分为正常,分数越高,运动发育越好。

1.4 治疗后运动发育情况

所有患儿每天均给予了维生素 D 400 IU,对于发育迟缓患儿每天给予维生素 D 800 IU~1200 IU 补充,治疗 3 个月,再做 Gesell 测评评估其运动发育水平,对比治疗后运动发育情况。

1.5 相关性分析

对比 ALP、25(OH)D3 都影响儿童运动发育迟缓的主要因素。

1.6 统计方法

所有新生儿数据都分组录入和复核，均需要二次录入,并核对、校正,使用 SPSS 22.00 软件进行数据统计分析,计量资料以均数±标准差表示,计数数据采用率、构成比与百分比表示,对比方法涉及 t 检验、卡方 χ^2 分析等,相关分析采用 Pearson 分析,多因素分析采用二分类多因素条件 Logistic 分析,按 α=0.05 水准,P<0.05 为对比差异有统计学意义。

2 结果

2.1 运动发育迟缓情况

在 500 例小儿中,判断为运动发育迟缓 120 例(迟缓组),占比 24.0 %。两组小儿的性别、胎龄、分娩方式、出生体重、头围、身长等对比差异无统计学意义(P>0.05),见表 1。

表 1 两组一般资料对比

Table 1 Comparison of general data between two groups

Groups	n	Gender (M/F)	Gestational age (weeks)	Mode of delivery (cesarean section / smooth delivery)	Birth weight(g)	Head circumference (cm)	Height(cm)
Delayed group	120	63/57	38.29±1.48	40/80	2519.4±298.4	33.39±1.49	46.29±2.58
Non-delayed group	380	197/183	38.20±2.19	124/256	2584.2±300.8	33.20±2.10	46.82±2.27

2.2 血清 ALP 与 25(OH)D3 水平对比

迟缓组的血清 ALP 水平高于非迟缓组,25(OH)D3 水平低于非迟缓组,对比差异均有统计学意义(P<0.05),见表 2。

2.3 运动发育评分对比

迟缓组的大动作、精细运动、适应性行为、语言、个人社交评分都低于非迟缓组,对比差异均有统计学意义(P<0.05),见表 3。

2.4 治疗后运动发育情况

非迟缓组干预前后大动作、精细运动、适应性行为、语言、个人社交评分无差异(P>0.05);迟缓组治疗后,大动作、精细运动、适应性行为、语言、个人社交评分均显著升高,对比差异均有统计学意义(P<0.05),见表 4。

2.5 相关性分析

Pearson 分析显示 ALP、25(OH)D3 与小儿运动迟缓发育具有相关性(P<0.05),见表 5。

在二分类多因素条件 Logistic 分析中,赋值运动发育迟缓

=1，非运动发育迟缓 =0，以 ALP、25(OH)D3 作为自变量，结果显示 ALP、25 (OH)D3 都影响儿童运动发育迟缓的主要因素（P<0.05），见表 6。

表 2 两组血清 ALP 与 25(OH)D3 水平对比（$\bar{x}\pm s$）

Table 2 Comparison of serum ALP and 25(OH)D3 levels between two groups（$\bar{x}\pm s$）

Groups	n	ALP(U/L)	25(OH)D3(nmol/L)
Delayed group	120	178.42±13.84*	25.09±3.11*
Non-delayed group	380	234.87±22.77	32.04±2.44

Note: Compared with the non-delayed group, *P<0.05.

表 3 两组运动发育评分对比（分，$\bar{x}\pm s$）

Table 3 Comparison of motor development scores between two groups (scores, $\bar{x}\pm s$)

Groups	n	Big action	Fine movement	Adaptive behavior	Talking	Personal social networking
Delayed group	120	74.38±15.28*	63.78±15.45*	55.49±15.29*	52.33±15.34*	64.47±15.23*
Non-delayed group	380	96.59±15.39	98.89±15.56	95.65±15.67	89.42±15.46	88.82±15.31

表 4 两组治疗前后运动发育情况（分，$\bar{x}\pm s$）

Table 4 Motor development before and after treatment of two groups (scores, $\bar{x}\pm s$)

Groups		Big action	Fine movement	Adaptive behavior	Talking	Personal social networking
Delayed group (n=120)	Pretherapy	74.38±15.28*	63.78±15.45*	55.49±15.29*	52.33±15.34*	64.47±15.23*
	Post-treatment	88.46±15.21	81.24±15.35	78.52±15.25	81.16±15.31	82.37±15.35
Non-delayed group (n=380)	Pretherapy	96.59±15.39	98.89±15.56	95.65±15.67	89.42±15.46	88.82±15.31
	Post-treatment	97.02±15.24	98.93±15.33	95.86±15.43	90.32± 15.41	89.53±15.25

表 5 儿童运动发育迟缓与血清 ALP、25(OH)D3 表达水平的相关性(n=120)

Table 5 Correlation between children's motor development delay and serum ALP and 25(OH)D3 expression levels (n=120)

Index	ALP	25(OH)D3
r	0.488	0.544
P	0.014	0.008

表 6 影响儿童运动发育迟缓的多因素分析(n=120)

Table 6 Analysis of multiple factors affecting children's motor retardation (n=120)

Factor	B	Wald	P	OR	95%CI
ALP	2.057	40.278	0.000	7.824	4.144-14.134
25(OH)D3	1.174	15.757	0.000	3.235	1.818-5.778

3 讨论

儿童运动发育迟缓是严重危害我国儿童健康的疾病之一，早期发现和诊断是改善预后的关键[13]。并且随着运动发育迟缓小儿存活率的明显提高，其生存质量越来越受到关注。本研究显示在 500 例小儿中，判断为运动发育迟缓 120 例(迟缓组)，两组小儿的性别、胎龄、分娩方式、出生体重、头围、身长等对比差异无统计学意义，表明儿童运动发育迟缓比较常见。

本研究显示迟缓组的血清 ALP 水平高于非迟缓组，25(OH)D3 水平低于非迟缓组。从机制上分析，维生素 D 是全球各国家的儿科医生都建议在幼儿生长发育过程中进行补充的物质，推荐足月儿每日补充维生素 D 400 IU 左右，早产儿、低出生体重儿应每日补充维生素 D 800 IU 左右[14,15]。各种原因造成的幼儿维生素 D 缺乏，是导致儿童运动发育迟缓的最主要原因之一。早产儿、药物滥用、冬季阳光暴露少等都易导致维生素 D 缺乏，也容易诱发肥胖症、高胆固醇血症等疾病的发生[16]。维生素 D 是机体内固有的一种类固醇激素，不仅能够维持机体的整体功能，同时还能起到抗分化、抑制炎症因子释放、介导免疫反应等作用[17,18]。本研究迟缓组的大动作、精细运动、适应性行为、语言、个人社交评分都低于非迟缓组，迟缓组补充维生素 D 治疗后，其大动作、精细运动、适应性行为、语言、个人社交评分等均显著升高。与吕楠[19]等学者的研究类似，该学者探讨维生素 AD 在运动发育迟缓患儿康复治疗中的作用，指导临床治疗，结果显示治疗后，维生素 D 组和维生素 AD 组的精细运动功能评分，Gesell 发育量表评估均高于对照组。说明补充维生素 D 可以显著的改善患儿的发育迟缓。

血清 25(OH)D3 是反映体内维生素 D 营养状况的指标，可通过参与 Th1/Th2 类细胞因子的免疫调节来调控机体的免疫偏移作用，还可调节多种炎症细胞因子表达[20]。ALP 是公认的机体组织破坏与修复的敏感指标，ALP 增加可导致机体容易发生感染，也是机体炎症因子大量释放后最早可被检测的客观物质指标之一[21]。ALP 活性检测对儿童运动发育迟缓早期诊断有准确、操作简单、敏感、特异等优点，有利于运动发育迟缓早期发现、早期诊断、早期防治。ALP 活性检测与 25(OH)D3 检测相结合是确诊和诊治儿童运动发育迟缓的良好策略[22,23]。当前也有研究表明 ALP 主要由骨细胞合成，当小儿体内 25(OH)D3 缺乏，出现骨钙化不足，其成骨细胞活跃，可导致 ALP 升高；而当成骨细胞转变为骨细胞，ALP 水平可逐渐下降[24,25]。

维生素 D 为脂溶性维生素，是小儿生长和发育所必需的维生素，维生素 D 缺乏易引发生长中骨骼成骨不良与钙磷代谢失常[26,27]。维生素 D 也可通过维生素 D 受体和维生素 D 结合蛋白协同作用，广泛参与炎症、基因调控、免疫等作用，孕妇低水平的维生素 D 水平可增加早产儿的发生率[28,29]。并且在儿童发育迟缓的生物学发病期，ALP 活性已开始升高[30,31]。本研究 Pearson 分析显示 ALP、25(OH)D3 与小儿运动迟缓发育具有相关性；二分类多因素条件 Logistic 分析结果显示 ALP、25(OH)D3 都是影响儿童运动发育迟缓的主要因素。当前有研究显示 ALP 的改变，先于骨骼影像学变化，并且与发育迟缓的病情成正相关，可精确反映发育迟缓早期病变[32]。而当小儿体内维生素 D 缺乏时，骨钙化不良，成骨细胞活跃，ALP 活性可显著上升[33]。但是本文中 ALP、25(OH)D3 对儿童运动发育迟缓的具体机制还没有进行阐述，将在下一步进行深入的机制分析。

总之，儿童运动发育迟缓与血清 ALP、25(OH)D3 水平存在相关性，两者的联合检测可为儿童发育迟缓的早期诊断提供实验依据，经过维生素 D 治疗后，能显著的改善其患儿的运动发育状态，具有很好的临床应用价值。

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