

· 其他肝病 ·

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胆汁淤积性肝病患儿的维生素D水平及临床特点

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摘要: 目的 分析胆汁淤积性肝病患儿的维生素D水平,为该病患儿补充维生素D治疗提供理论依据。方法 选取2022年1月—2024年1月于首都医科大学附属北京儿童医院中医科初次就诊的胆汁淤积性肝病患儿116例,按照性别、年龄、补充维生素D剂量、病程、病因分别进行分组比较,并收集患儿的血清25-羟维生素D(25-OH-D)水平及相关生化指标,分析维生素D水平与生化指标的相关性。计数资料组间比较采用 χ^2 检验或Fisher精确概率法。相关分析采用Spearman秩相关。**结果** 116例患儿中76例(65.5%)存在维生素D缺乏或不足。维生素D缺乏或不足在男性中占65.7%(46/70),在女性中占65.2%(30/46),差异无统计学意义($\chi^2=0.003, P=0.956$)。维生素D缺乏或不足在从未补充过维生素D患儿中占83.3%(25/30),在每日补充500 IU者中占58.7%(27/46),在每日补充700 IU者中占64.3%(18/28),在每日补充>700 IU者中占50.0%(6/12),差异无统计学意义($\chi^2=6.460, P=0.091$)。不同病因比较结果显示,维生素D缺乏或不足在感染性疾病组占57.7%(15/26),在遗传代谢性疾病组占66.7%(10/15),在药物性肝损伤组占66.7%(6/9),在胆道系统结构异常组占100.0%(8/8),在病因未明组占63.8%(37/58),差异无统计学意义($\chi^2=5.304, P=0.252$)。不同病程比较结果显示,维生素D缺乏或不足在<1个月组占78.4%(29/37),在1~3个月组占54.3%(25/46),在>3~6个月组占53.3%(8/15),在>6个月组占77.8%(14/18),差异无统计学意义($\chi^2=7.432, P=0.059$)。不同年龄段比较结果显示,儿童组维生素D缺乏或不足占比明显高于婴儿组(82.5% vs 52.5%, $\chi^2=9.504, P=0.018$)。相关性分析结果显示,血清AST、ALT与25-OH-D无显著相关性(P 值均>0.05);血清ALP($r=-0.286, P=0.002$)、GGT($r=-0.248, P=0.007$)、TBil($r=-0.353, P<0.001$)、DBil($r=-0.299, P=0.001$)、总胆汁酸($r=-0.236, P=0.011$)与25-OH-D均呈负相关;血清钙($r=0.263, P=0.004$)、磷($r=0.385, P<0.001$)与25-OH-D均呈正相关。**结论** 大部分胆汁淤积性肝病患儿存在维生素D缺乏或不足;血清ALP、GGT、TBil、DBil或总胆汁酸水平升高,钙或磷水平降低,对维生素D缺乏或不足具有提示作用。

关键词: 胆汁淤积; 维生素D; 儿童**基金项目:** 国家自然科学基金(82205184);北京市属医院科研培育计划(PZ2022027)

Level of vitamin D in children with cholestatic liver disease and its clinical features

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Abstract: Objective To investigate vitamin D level in children with cholestatic liver disease, and to provide a theoretical basis for vitamin D supplementation therapy in children with this disease. **Methods** A total of 116 children with cholestatic liver disease who attended Department of Traditional Chinese Medicine, Beijing Children's Hospital, Capital Medical University, for the first time from January 2022 to January 2024 were enrolled and divided into groups for comparison based on sex, age, vitamin D supplementation dose, course of the disease, and etiology. The data on the serum level of 25-hydroxyvitamin D (25-OH-D) and related biochemical parameters were collected to assess the correlation between vitamin D level and biochemical parameters. The chi-square test or the Fisher's exact test was used for comparison of categorical data between groups, and the Spearman rank

correlation test was used for correlation analysis. **Results** Among the 116 children, 76 (65.5%) had vitamin D deficiency or insufficiency. The children with vitamin D deficiency or insufficiency accounted for 65.7% (46/70) among boys and 65.2% (30/46) among girls, with no significant difference between boys and girls ($\chi^2=0.003$, $P=0.956$). The children with vitamin D deficiency or insufficiency accounted for 83.3% (25/30) among the children who had never received vitamin D supplementation, 58.7% (27/46) among the children with a daily supplementation dose of 500 IU, 64.3% (18/28) among the children with a daily supplementation dose of 700 IU, and 50.0% (6/12) among the children with a daily supplementation dose of >700 IU, and there was no significant difference between these groups ($\chi^2=6.460$, $P=0.091$). Comparison between the groups with different etiologies showed that the children with vitamin D deficiency or insufficiency accounted for 57.7% (15/26) in the infectious disease group, 66.7% (10/15) in the inherited metabolic disease group, 66.7% (6/9) in the drug-induced liver injury group, 100.0% (8/8) in the group with abnormal structure of the biliary system, and 63.8% (37/58) in the group with unknown etiology, and there was no significant difference between these groups ($\chi^2=5.304$, $P=0.252$). Comparison between the groups with different courses of the disease showed that the children with vitamin D deficiency or insufficiency accounted for 78.4% (29/37) in the <1 month group, 54.3% (25/46) in the 1—3 months group, 53.3% (8/15) in the 3—6 months group, and 77.8% (14/18) in the >6 months group, with no significant difference between these groups ($\chi^2=7.432$, $P=0.059$). Comparison between different age groups showed that compared with the infant group, the children group had a significantly higher proportion of children with vitamin D deficiency or insufficiency ($\chi^2=9.504$, $P=0.018$). The correlation analysis showed that serum aspartate aminotransferase and alanine aminotransferase had no significant correlation with 25-OH-D ($P>0.05$); serum alkaline phosphatase (ALP) ($r=-0.286$, $P=0.002$), gamma-glutamyl transpeptidase (GGT) ($r=-0.248$, $P=0.007$), total bilirubin (TBil) ($r=-0.353$, $P<0.001$), direct bilirubin (DBil) ($r=-0.299$, $P=0.001$), and total bile acid ($r=-0.236$, $P=0.011$) were negatively correlated with 25-OH-D, while serum calcium ($r=0.263$, $P=0.004$) and phosphorus ($r=0.385$, $P<0.001$) were positively correlated with 25-OH-D. **Conclusion** Most children with cholestatic liver disease have vitamin D deficiency or insufficiency, and the increase in serum ALP, GGT, TBil, DBil or total bile acid and the reduction in calcium or phosphorus may suggest vitamin D deficiency or insufficiency.

Key words: Cholestasis; Vitamin D; Child

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胆汁淤积性肝病是各种原因导致的以胆汁淤积为主要表现的肝胆疾病的统称^[1]。胆汁淤积是指肝内外各种原因造成胆汁形成、分泌或排泄障碍,可导致肝细胞损伤,肠道内胆汁减少,影响肠道的消化、吸收功能^[2]。胆汁调节肠道对脂肪和脂溶性维生素的吸收,因而胆汁淤积时,常存在脂肪和脂溶性维生素(维生素A、D、E和K)的吸收缺陷^[3],造成婴幼儿及青少年营养不良。维生素D是生长发育所需的重要物质,25-羟基维生素D(25-OH-D)是其在体内的活性代谢产物,可反映机体维生素D的水平。近年来,维生素D与胆汁淤积性肝病的关系成为研究的热点,本研究对胆汁淤积性肝病患儿维生素D水平进行评估,分析不同性别、年龄、补充维生素D剂量、病程、病因的胆汁淤积性肝病患儿维生素D水平差异,并进行25-OH-D与生化指标的相关性分析,为胆汁淤积患儿维生素D的补充治疗提供依据。

1 资料与方法

1.1 研究对象 选择2022年1月—2024年1月于首都

医科大学附属北京儿童医院中医科初次就诊的胆汁淤积性肝病患儿。纳入标准:DBil>17.1 $\mu\text{mol/L}$,且DBil占TBil比例>20%^[4]。排除标准:合并肝脏以外的其他影响维生素D吸收的疾病,如合并慢性肾病、炎症性肠病、恶性肿瘤等。

1.2 临床资料采集 记录患儿的年龄、性别、病因、血清生化指标和补充维生素D剂量,其中生化指标包括ALP、GGT、25-OH-D、AST、ALT、TBil、DBil、总胆汁酸(TBA)、血清钙和磷。根据25-OH-D水平分为维生素D缺乏(<20 ng/mL)、维生素D不足(21~29 ng/mL)和维生素D充足(≥ 30 ng/mL)^[5]。

1.3 统计学方法 采用SPSS 27.0统计软件进行数据分析。计数资料组间比较采用 χ^2 检验或Fisher精确概率法。相关分析采用Spearman秩相关,以相关系数(r)评价变量间的相关性。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 一般资料 共纳入胆汁淤积性肝病患儿116例,其

中男70例,维生素D缺乏或不足46例(65.7%);女46例,维生素D缺乏或不足30例(65.2%)。维生素D缺乏或不足在性别上差异无统计学意义($\chi^2=0.003, P=0.956$)。所有患儿中,从未补充过维生素D者30例,维生素D缺乏或不足25例(83.3%);每日补充维生素D 500 IU者46例,维生素D缺乏或不足27例(58.7%);每日补充700 IU者28例,维生素D缺乏或不足18例(64.3%);每日补充>700 IU者12例,维生素D缺乏或不足6例(50.0%)。维生素D缺乏或不足在补充不同维生素D剂量上差异无统计学意义($\chi^2=6.460, P=0.091$)。

2.2 不同年龄组患儿维生素D缺乏或不足的比较 将纳入的116例患儿按照年龄划分为婴儿组(<1岁)、幼儿组(1~3岁)、儿童组($\geq 3\sim 12$ 岁)和青春期组($\geq 12\sim 18$ 岁)。不同年龄组患儿的维生素D缺乏或不足所占百分比差异有统计学意义($\chi^2=10.209, P=0.012$);进一步比较发现,婴儿组与儿童组维生素D缺乏或不足所占百分比差异有统计学意义($\chi^2=9.504, P=0.018$)(表1)。

表1 不同年龄组患儿维生素D缺乏或不足的比较

Table 1 Comparison of vitamin D deficiency or insufficiency in different age groups

组别	例数	维生素D缺乏或不足[例(%)]
婴儿组	61	32(52.5)
幼儿组	5	4(80.0)
儿童组	40	33(82.5) ¹⁾
青春期组	10	7(70.0)
χ^2 值		10.209
P值		0.012

注:与婴儿组比较,1)P<0.05。

2.3 不同病程患儿维生素D缺乏或不足的比较 按照病程将116例胆汁淤积性肝病患儿分为<1个月组、1~3个月组、>3~6个月组以及>6个月组。结果显示,不同病程患儿的维生素D缺乏或不足所占百分比差异无统计学意义($P>0.05$)(表2)。

表2 不同病程患儿维生素D缺乏或不足的比较

Table 2 Comparison of vitamin D deficiency or insufficiency in different disease course groups

组别	例数	维生素D缺乏或不足[例(%)]
<1个月组	37	29(78.4)
1~3个月组	46	25(54.3)
>3~6个月组	15	8(53.3)
>6个月组	18	14(77.8)
χ^2 值		7.432
P值		0.059

2.4 不同病因患儿维生素D缺乏或不足的比较 按照不同病因进行分组,其中感染性疾病组26例,主要为巨细胞病毒感染(88.5%),少数为细菌感染;遗传代谢性疾病组15例,包括Alagille综合征、希特林蛋白缺乏症、

进行性家族性肝内胆汁淤积症、肝豆状核变性和Dubin-Johnson综合征;药物性肝损伤组9例,主要由异烟肼、利福平、布洛芬或阿莫西林等药物导致;胆道系统结构异常组8例,包括胆道闭锁、先天性胆总管囊肿、胆总管结石、先天性门静脉畸形等;病因未明组58例。不同病因患儿的维生素D缺乏或不足所占百分比差异无统计学意义($P>0.05$)(表3)。

表3 不同病因患儿维生素D缺乏或不足的比较

Table 3 Comparison of vitamin D deficiency or insufficiency in different etiologic groups

组别	例数	维生素D缺乏或不足[例(%)]
感染性疾病组	26	15(57.7)
遗传代谢性疾病组	15	10(66.7)
药物性肝损伤组	9	6(66.7)
胆道系统结构异常组	8	8(100.0)
病因未明组	58	37(63.8)
χ^2 值		5.304
P值		0.252

2.5 血清25-OH-D水平与生化指标的相关性分析 血清ALP($r=-0.286, P=0.002$)、GGT($r=-0.248, P=0.007$)、TBil($r=-0.353, P<0.001$)、DBil($r=-0.299, P=0.001$)、TBA($r=-0.236, P=0.011$)与25-OH-D均呈负相关;血清钙($r=0.263, P=0.004$)、磷($r=0.385, P<0.001$)与25-OH-D均呈正相关;25-OH-D与血清AST($r=0.038, P=0.684$)和ALT($r=-0.025, P=0.793$)未见显著相关性。

3 讨论

维生素D包括维生素D₂和维生素D₃。在肝脏中,维生素D₃被部分胆固醇羟化酶转化为25-OH-D,其在血清中相对稳定,半衰期长,含量高,被作为检测维生素D的最佳指标^[6]。研究^[7-9]表明,维生素D与多种肝病的发生发展和治疗预后密切相关。据报道^[10-12],患有慢性肝病的儿童维生素D缺乏率较高,且胆汁淤积越严重,维生素D水平越低。本研究中,仅有30例患儿从未补充过维生素D,但维生素D缺乏或不足占比达65.5%(76/116),其原因可能为胆汁淤积时,肠内胆盐减少,造成脂溶性维生素吸收降低^[13]。补充不同维生素D剂量分析结果显示,常规补充剂量无法满足胆汁淤积性肝病患儿机体需要。此外,不同病程患儿的维生素D缺乏或不足占比差异亦无统计学意义($P>0.05$),原因可能为病因复杂,所纳入病例发展缓慢,无发展成肝硬化、肝纤维化等重症者。

既往研究^[8,12]表明,婴儿胆汁淤积性肝病维生素D缺乏或不足占比为88.1%~88.43%,患有慢性肝病的儿童维生素D缺乏症患病率为27.1%~78.9%^[11,14]。而本研究结果中,婴儿组维生素D缺乏或不足占比为52.5%,

儿童组占比为82.5%,高于婴儿组,可能因为随着年龄增加,维生素D制剂补充率降低,且儿童中规律补充维生素D制剂的比例也较低。据调查,我国儿童维生素D缺乏率随着年龄增加逐渐增高,儿童应在医生指导下常规给予预防剂量的维生素D补充剂,有助于降低维生素D缺乏的风险^[15-16]。美国儿科学会已建议新生儿即开始补充维生素D,并持续至青春期^[17]。国内指南^[18]建议儿童维生素D的摄入量至少为400 U/d,应将25-OH-D水平维持在30 ng/mL以上^[19]。

本研究表明,维生素D缺乏或不足与胆汁淤积性肝病患者的病因无关。胆汁淤积性肝病的病因复杂,在本研究中以感染因素最多见,主要为巨细胞病毒感染。研究^[20]表明,25-OH-D水平与巨细胞病毒感染预后密切相关,临床上可通过密切监测其水平来评估巨细胞病毒感染及预后。本研究中遗传代谢性疾病是胆汁淤积性肝病的主要病因之一,遗传代谢性疾病常合并脂溶性维生素缺乏,因此补充脂溶性维生素已作为该类疾病的常规治疗手段^[21]。肝损伤是异烟肼、利福平等药物最常见的副作用之一,抗结核药物造成肝损伤的具体机制尚不清楚,可能与药物反应性代谢物诱导肝细胞氧化应激、线粒体损伤有关。研究^[22-23]发现,维生素D缺乏与促进肝脏氧化应激有关,维生素D缺乏会导致线粒体呼吸紊乱,活化的维生素D是维持线粒体呼吸链生理活性的重要成分,其通过维持线粒体的功能,支持细胞对氧化还原的控制。胆管系统结构异常是维生素D缺乏的高危因素,如胆道闭锁患儿更容易出现维生素D缺乏,原因包括吸收不足和羟化不足,因此大多数医疗中心建议补充维生素D直至达到正常参考值水平,甚至应该在规律监测的前提下增加维生素D的补充剂量^[24-27]。

本研究显示,胆汁淤积性肝病患儿血清25-OH-D水平与ALP、GGT、TBil、DBil、TBA呈负相关。ALP、GGT、TBil、DBil、TBA是诊断胆汁淤积性肝病和判断预后的主要生化指标。动物实验^[28]发现,维生素D可减轻梗阻性胆汁淤积性损伤和肝细胞损伤。TBil、DBil、TBA、ALP和GGT水平明显增高,即存在胆汁淤积时,需要警惕维生素D的缺乏。李婧等^[29]研究亦认为胆汁淤积性肝病患儿血清TBil、DBil、TBA水平升高对维生素D₃缺乏有提示作用。研究^[30]发现维生素D水平与肝病严重程度之间存在负相关性,且以维生素D为基础的治疗在防止肝病进展和改善治疗反应方面具有潜力^[31]。有实验^[32]表明补充维生素D₃可减轻硫代乙酰胺引起的大鼠肝毒性及纤维化,主要是通过降低TBil、DBil、ALT、AST和ALP水平,增加25-OH-D₃来缓解升高的肝功能指标。维生素D参与调节钙磷代谢,能促进钙、磷在肠道的吸收,维持血清钙和磷水平正常^[19]。本研究表明,血清25-OH-D水平与钙、磷具有相关性,与目前的认知一致。

综上,维生素D缺乏常见于胆汁淤积性肝病患儿,且临床容易被忽视。血清生化指标对胆汁淤积性肝病患儿的维生素D水平起到提示作用。当临床中发现患儿ALP、GGT、TBil、DBil、TBA显著升高或钙、磷降低时,需要警惕维生素D的缺乏或不足。目前,在预防、监测和治疗胆汁淤积性肝病的维生素D缺乏方面,缺乏统一的儿科指南。鉴于胆汁淤积性肝病是维生素D缺乏的重要风险因素,临床医生应保持警惕,动态监测维生素D水平,以及时补充治疗。

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