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高胆红素血症新生儿肠道菌群特点与苯巴比妥治疗效果的相关性 *

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摘要 目的:探讨与分析高胆红素血症新生儿肠道菌群特点与苯巴比妥治疗效果的相关性。**方法:**选择2020年6月到2022年6月在本院诊治的565例高胆红素血症新生儿作为研究对象,所有患儿都给予苯巴比妥治疗,检测新生儿肠道菌群与血清α-谷胱甘肽-s-转移酶(α-GST)、肌酸激酶同工酶(CK-MB)、胆红素含量,判定患儿的治疗效果并进行相关性分析。**结果:**565例患儿治疗7 d后,有效490例(有效组),有效率为86.7%。有效组的血清胆红素、经皮胆红素含量都明显低于无效组(P<0.05)。有效组的血清α-GST、CK-MB含量都明显低于无效组(P<0.05)。有效组的肠球菌属、埃希氏菌属、链球菌属相对丰度均低于无效组,拟杆菌属相对丰度明显高于无效组(P<0.05)。在565例患儿中,Spearsman分析显示苯巴比妥治疗效果有效与肠球菌属、埃希氏菌属、链球菌属、拟杆菌属相对丰度都呈现相关性(P<0.05)。**结论:**苯巴比妥治疗新生儿高胆红素血症的效果有待提高,通过胆红素、α-GST、CK-MB、肠道菌群检测能有效判定患儿的治疗效果,同时肠道菌群与治疗效果存在相关性。

关键词:苯巴比妥;新生儿;高胆红素血症;肠道菌群
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Correlation between Intestinal Microbiota Characteristics and The Effect of Phenobarbital Treatment in Newborns with Hyperbilirubinemia*

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ABSTRACT Objective: To explore and analyze the correlation of gut flora characteristics and the effect of phenobbilbital treatment in newborns with hyperbilirubinemia. **Methods:** From June 2020 to June 2022, A total of 565 neonates with hyperbilirubinemia who were diagnosed and treated in our hospital from were selected as the research subjects. All the cases were treated with phenobarbital, The neonatal intestinal flora were detected, and serum α-glutathione-s-transferase (α-GST), creatine kinase isoenzyme (CK-MB), bilirubin levels were detected, and were to determine the patient with cases' treatment effect and correlation analysis. **Results:** After 7 days of treatment in 565 neonatesn, there were 490 cases were effective (effective group), and the effective rate was 86.7 %. The contents of serum bilirubin and transdermal bilirubin in the effective group were lower than those in the ineffective group (P<0.05). The serum α-GST and CK-MB levels in the effective group were lower than those in the ineffective group (P<0.05). The relative abundances of Enterococcus, Escherichia and Streptococcus in the effective group were higher in the ineffective group, and the relative abundance of Bacteroides was higher than that in the ineffective group (P<0.05). In the 565 neonates, Spearsman analysis showed that the treatment effect of phenobarbital treatment was correlated with the relative abundances of Enterococcus, Escherichia, Streptococcus and Bacteroides (P<0.05). **Conclusion:** The effect of phenobarbital in the treatment of neonatal hyperbilirubinemia needs to be improved. The detection of bilirubin, α-GST, CK-MB can effectively determine the treatment effect of children with intestinal flora, and there is a correlation between intestinal flora and the treatment effect.

Key words: Phenobarbital; Neonates; Hyperbilirubinemia; Intestinal flora
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前言

高胆红素血症指当胆红素生成率超过其清除率时,出现临床表现[1]。高胆红素血症多发生于新生儿,需要及时展开对症治疗,以防止患儿出现躯体脏器、免疫系统、中枢神经系统、血液系统损伤[2,3]。特别是由于部分地区对新生儿高胆红素血症缺乏足够的认识,也使得胆红素中枢神经系统损伤的发生率仍然较高。苯巴比妥能减少胆红素的肝-肠循环,增加血清胆红素清除,减少胆红素在肠道的重吸收,促进胆汁排出[4]。但由于新生儿内环境比较复杂,单纯使用苯巴比妥治疗的效果一直有待提

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高，为此有效预测患儿的治疗效果具有重要价值[5,6]。正常人体中肠道菌群包含大约 2 万个菌种，在维护肠壁的运动及其灌注和通透性等方面发挥了重要作用，也参与调控多种不同的肠道相关生理功能[7,8]。在新生儿时期，当出现胃肠道微生物群的延迟定居和非结合胆红素在肠道内累积时，肠道内 β- 葡萄糖醛酸苷酶会发生异常，对新生儿胆红素代谢产生负面影响，从而诱发高胆红素血症的发生[9,10]。本文探讨与分析了高胆红素血症新生儿肠道菌群特点与苯巴比妥治疗效果的相关性，以促进明确高胆红素血症的发生机制，为早期预测患儿治疗效果提供参考。现报道如下。

1 资料与方法

1.1 一般资料

选择 2020 年 6 月到 2022 年 6 月在本院诊治的 565 例高胆红素血症新生儿作为研究对象。

纳入标准：符合高胆红素血症的诊断标准；日龄 1 d-12 d；产妇年龄≤40 岁；临床资料完整；新生儿家长知情同意本研究；经医院伦理委员会的批准；新生儿出生时无产伤窒息；临床表现为皮肤黄染、血清总胆红素增高等。

排除标准：先天遗传代谢疾病、先天畸形患儿；合并高危呼吸道传染性疾病的患儿；临床资料缺乏者；伴有头颅血肿等疾病的患儿。

1.2 治疗方法

所有患儿都给予苯巴比妥治疗，每次口服（上海信宜药厂有限公司，国药准字 H31022038）2.5 mg/kg，2 次 /d，治疗观察 7 d。

1.3 有效标准判定

有效标准：患儿黏膜、皮肤黄染等症状大部分消失，血清胆红素水平位于 Bhutani 曲线第 40 百分位数以下，且饮食及精神状态大部分恢复正常。

1.4 观察指标

（1）观察与记录所有患儿的日龄、胎龄、性别、体重、娩出方式等指标。

（2）所有患儿在治疗前抽取静脉血 1 mL，在 3000 转 / 分钟下离心 10 min，取上层血清。采用全自动生化分析仪测定与记录血清胆红素、经皮胆红素水平，检测试剂盒购自武汉三鹰公司。采用酶联免疫法检测 α- 谷胱甘肽 -s- 转移酶（α-Glutathione-S-transferase, α-GST）、肌酸激酶同工酶（Creatine kinase isoenzyme, CK-MB）水平，检测试剂盒购自上海酶联公司。

（3）提取所有新生儿的治疗前早晨新鲜粪便，提取基因组 DNA，然后进行 16S rRNA PCR 扩增，采用琼脂糖凝胶电泳检测 PCR 产物，然后给予 Illumina MiSeq 高通量测序仪进行测序。测序后进行序列拼接与生物信息学分析，基于有效数据进行聚类和物种分类分析，目的菌群属水平相对丰度 = 目的菌群的基因拷贝数 / 总拷贝数。

1.5 统计方法

选择 SPSS19.00 进行分析，计量数据表示为均数± 标准差，计数数据表示为%与构成比等，对比采用 t 检验与卡方 x^2 分析，相关性分析采用 Spearsman 分析，检验水准为 α=0.05。

2 结果

2.1 治疗效果

565 例患儿经过 7 d 治疗后，有效 490 例（有效组），有效率为 86.7 %。

2.2 一般资料对比

有效组一般资料与无效组对比无明显差异（P>0.05）。见表1。

表 1 一般资料对比

Table 1 The comparison of the general data

Groups	n	Age in days (d)	Fetal age (week)	Gender (male / female)	Weight (kg)	Delivery method (natural delivery / cesarean section)
Effective group	490	5.69± 0.24	39.15± 1.11	251/239	3.74± 0.22	310/180
Invalid group	75	5.62± 0.33	39.87± 0.98	38/37	3.78± 0.18	45/30

表 2 两组血清胆红素、经皮胆红素含量对比（μmol/L，均数± 标准差）

Table 2 Comparison of serum bilirubin and percutaneous bilirubin content (μmol/L, mean ± standard deviation)

Groups	n	Serum bilirubin	Percutaneous bilirubin
Effective group	490	214.65± 14.92#	209.87± 14.87#
Invalid group	75	256.09± 15.02	245.09± 11.09

Note: Compared with invalid group, #P<0.05, the same below.

2.3 血清胆红素、经皮胆红素含量对比

有效组的血清胆红素、经皮胆红素含量低于无效组（P<0.05）。见表 2。

2.4 血清 α-GST、CK-MB 含量对比

有效组的血清 α-GST、CK-MB 含量低于无效组（P<0.05）。见表 3。

2.5 肠道菌群相对丰度对比

有效组的肠球菌属、埃希氏菌属、链球菌属相对丰度低于无效组，拟杆菌属相对丰度高于无效组（P<0.05）。见表 4。

2.6 相关性分析

在 565 例患儿中，Spearsman 分析显示苯巴比妥治疗效果与肠球菌属、埃希氏菌属、链球菌属、拟杆菌属相对丰度都呈现相关性（P<0.05）。见表 6。

表 3 两组血清 α-GST、CK-MB 含量对比(均数± 标准差)

Table 3 Comparison of serum α -GST and CK-MB content between the two groups (mean ± standard deviation)

Groups	n	α-GST(μg/L)	CK-MB(U/L)
Effective group	490	31.66± 2.38#	45.87± 2.22#
Invalid group	75	38.47± 3.01	51.73± 3.87

表 4 两组肠道菌群相对丰度对比(均数± 标准差)

Table 4 Comparison of relative abundance of two intestinal flora groups (mean ± standard deviation)

Groups	n	Enterococcus	Escherichia	Streptococcus	Bacaeroides
Effective group	490	1.21± 0.22#	5.55± 0.24#	1.45± 0.18#	0.97± 0.13#
Invalid group	75	1.67± 0.14	7.28± 0.33	2.54± 0.24	0.34± 0.05

表 6 高胆红素血症新生儿肠道菌群特点与苯巴比妥治疗效果的相关性(n=565)

Table 6 Correlation between intestinal microbiota characteristics and the effect of phenobarbital treatment in newborns with hyperbilirubinemia (n=565)

Indexs	Enterococcus	Escherichia	Streptococcus	Bacaeroides
r	-0.666	-0.585	-0.633	0.692
P	0.000	0.000	0.000	0.000

3 讨论

高胆红素血症临床表现为皮肤、巩膜等黄染，与胆红素排泄障碍、胆红素生成过多、胆红素结合能力降低等有关[12]。高胆红素血症在足月儿、早产儿中的发病率较高，生理性黄疸可自行消退。但是病理性黄疸可对患儿大脑及多个脏器造成损伤，需要及时进行早期干预，以预防严重并发症的发生[13]。当前临床可采用血清胆红素、经皮胆红素水平对高胆红素血症进行检测，利于及时了解新生儿的病情，并对其实施准确诊断，也有利于指导临床进行治疗[14,15]。本研究显示 565 例患儿经过 7 d 治疗后，有效 490 例(有效组)，有效率为 86.7 %；有效组的日龄、胎龄、性别、体重、娩出方式等与无效组对比无明显差异(P>0.05)；有效组的血清胆红素、经皮胆红素含量都明显低于无效组(P<0.05)，表明苯巴比妥治疗新生儿高胆红素血症的效果有待提高，通过胆红素检测能有效判定患儿的治疗效果，预防血清胆红素过高导致胆红素脑病等神经系统病变的发生。分析可知，苯巴比妥可提高肝脏微粒体葡萄糖醛酸转移酶的活性，减少血浆胆红素水平，胆红素能够与葡萄糖醛酸进行结合，从而发挥治疗作用。但是胆红素检测的特异性有待提高，很难持续预测患儿的治疗效果[16,17]。

现代研究表明，新生儿时期可产生大量胆红素，如果由于内外在各种因素的负面影响，肝脏在摄取、结合、排泄方面存在障碍，可使得胆红素重过度吸收，从而引发高胆红素血症[18,19]。本研究显示有效组的血清 α-GST、CK-MB 含量都明显低于无效组(P<0.05)，表明通过血清 α-GST、CK-MB 检测能有效判定新生儿高胆红素血症苯巴比妥治疗的治疗效果。α- 谷胱甘肽 -s- 转移酶主要存在于胞液中，可有效反映机体的肝功能[20]。α-GST 有助于早期反映高胆红素血症患儿肝细胞损害情况，且具有更好的敏感性与特异性[21,22]。CK-MB 是心肌组织损害的敏感指标之一，主要存在于心肌组织中，可特异性反映心肌损伤情况[23,24]。苯巴比妥可抑制肠道中 β- 葡萄糖醛酸苷酶活性，苯巴比妥可降低胆红素肝肠循环反应，提高肝酶活性，增加结合胆红素，减轻胆红素损伤肝细胞，减轻炎症反应，可抑制血清 α-GST、CK-MB 的表达[25,26]。

人体肠道内分为正常菌群和致病菌，与人体健康最为密切的是肠球菌属、埃希氏菌属、链球菌属、拟杆菌属等[27]。肠道微生物对维持肠道屏障功能完整性、肠道发育以及免疫反应等有重要作用，特别是当前研究表明已有大量肠道菌群参与调节大脑的营养物质产生、突触形成、递质释放等过程。当新生儿肠道内无细菌或者出现细菌平衡被打破时，结合胆红素不能还原成尿胆原随粪便排出，可诱发高胆红素血症的发生[28,29]。肠道的微生物及其代谢产物在维持机体血清胆红素水平中具有重要作用，加强肠道代谢可降低血清胆红素表达[30]。机体代谢功能障碍与肠道菌群变化息息相关，肠道菌群可参与机体代谢，经改变肝功能调节胆红素的代谢，提高肝酶活性，完善免疫系统，促进胆红素的结合和排泄。本研究显示有效组的肠球菌属、埃希氏菌属、链球菌属相对丰度都低于无效组，拟杆菌属相对丰度明显高于无效组（P<0.05)；Spearsman 分析显示高胆红素血症新生儿苯巴比妥治疗效果与肠球菌属、埃希氏菌属、链球菌属、拟杆菌属相对丰度都呈现相关性(P<0.05)，表明经苯巴比妥治疗，高胆红素血症新生儿肠道菌群与效果存在相关性。分析可知，苯巴比妥能调节和改善肠道内菌群平衡，维持肠道正常功能。而拟杆菌属相对丰度增加可竞争性地阻止直接胆红素分解为间接胆红素，减少肠肝循环，有利于机体建立肠道正常菌群，促使结合胆红素还原成尿胆原随粪便排出。本研究存在一定不足，未对患儿治疗前后的肠道菌群情况进行分析，分组较少，观察时间较短，未具体分析不良反应发生情况，将在后续研究中探讨。

总之，苯巴比妥治疗新生儿高胆红素血症的效果有待提高，通过胆红素、α-GST、CK-MB、肠道菌群检测能有效判定患儿的治疗效果，同时肠道菌群与治疗效果存在相关性。

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