

· 临床研究 ·

早产儿与足月儿肺动脉高压的原发疾病调查

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[摘要] 目的:探讨新生儿肺动脉高压的相关高危因素。方法:收集近3年南京医科大学第一附属医院儿科收治的肺动脉高压新生儿41例,分为足月儿组和早产儿组,回顾性分析了两组的临床资料与新生儿肺动脉高压的关系。结果:早产儿组23例,足月儿组18例。早产儿组胎膜早破、胎盘早剥、绒毛膜羊膜炎、子痫的发生率高于足月儿组,差异有统计学意义($P < 0.05$)。足月儿组的孕母妊娠期糖尿病5例(占27.8%),早产儿组孕母妊娠期糖尿病共1例(占4.3%),与足月儿组比较,差异有统计学意义($\chi^2=4.437, P=0.035$)。与足月儿组相比,早产儿组的原发病以呼吸窘迫综合征为主($\chi^2=19.158, P < 0.001$),容易合并肺出血($\chi^2=4.433, P=0.035$)、颅内出血($\chi^2=8.715, P=0.003$)。足月儿组原发疾病主要为先天性心脏病(室间隔缺损)($\chi^2=10.786, P=0.001$)。新生儿肺炎在两组均有较高发生率,但差异无统计学意义($\chi^2=0.327, P > 0.05$)。两组之间并发代谢性酸中毒、新生儿低血糖、气胸、败血症等统计比较,差异无统计学意义($P > 0.05$)。早产儿组治愈21例,死亡2例,足月儿组治愈15例,死亡3例,治疗效果两组比较差异无统计学意义($P > 0.05$)。结论:早产儿肺动脉高压的高危原发疾病是呼吸窘迫综合征、重症肺炎、肺出血以及孕母有胎膜早破、胎盘早剥等并发症;患有先天性心脏病如室间隔缺损的足月儿,要重视可能伴有的肺动脉高压并及时诊治。

[关键词] 新生儿肺动脉高压;早产儿;足月儿;危险因素

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Investigations of primary diseases of pulmonary hypertension in preterm and full-term neonates

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[Abstract] **Objective:** This study aims to investigate the risk factors of pulmonary hypertension in neonates. **Methods:** From January 2017 to December 2019, 41 neonates with pulmonary hypertension admitted to the neonatal ward of the First Affiliated Hospital of Nanjing Medical University were collected and divided into preterm neonate group and full-term neonate group according to their gestational ages. The relationship between pulmonary hypertension and high risk factors such as primary disease and maternal high risk factors during pregnancy were analyzed retrospectively. **Results:** During the indicated three years, 1 992 premature infants and 3 394 full-term infants were collected. Among them, 23 premature (1.15%) and 18 full-term infants (0.53%) with pulmonary hypertension were included. There were significant differences in birth weight and gestational age between the two groups ($P < 0.05$). No statistical differences in maternal age, gender, mode of delivery, twin or multiple births, and Apgar scores between the two groups ($P > 0.05$). The incidences of premature rupture of membranes, placental abruption, chorioamnionitis and eclampsia in preterm group were higher than those in full-term group ($P < 0.05$). The differences were statistically significant in the incidences of gestational diabetes mellitus between the two groups (5 cases in full-term group vs. 1 case in preterm group, $\chi^2=4.437, P=0.035$). Compared with the full-term group, the major primary disease of preterm group was respiratory distress syndrome ($\chi^2=19.158, P < 0.001$), pulmonary hemorrhage ($\chi^2=4.433, P=0.035$) and intracranial hemorrhage ($\chi^2=8.715, P=0.003$), respectively. The primary disease in full-term group was mainly congenital heart disease (ventricular septal defect) ($\chi^2=10.786, P=0.001$). There was a high occurrence rate of neonatal pneumonia in both groups, but no statistical difference was shown ($\chi^2=0.327, P > 0.05$). There were no statistical differences in metabolic acidosis,

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neonatal hypoglycemia, pneumothorax and septicemia between the two groups ($P > 0.05$). In preterm group, 21 cases were cured and 2 cases died. 15 cases were cured and 3 cases died in full-term group. No statistical difference was found in treatment effect between the two groups ($P > 0.05$). **Conclusion:** The high-risk primary diseases of pulmonary hypertension in premature infants included respiratory distress syndrome, severe pneumonia, pulmonary hemorrhage, premature rupture of membranes and placental abruption. For full-term infants with congenital heart disease such as ventricular septal defect, timely diagnosis and treatment against pulmonary hypertension should be paid more attentions.

[Key words] pulmonary hypertension of neonates; premature infants; full-term infants; risk factor

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新生儿肺动脉高压是由多种因素导致的新生儿循环系统发生障碍的疾病,新生儿出现肺血管阻力增高和严重的低氧血症^[1-2]。严重的肺动脉高压常常危及新生儿生命,是新生儿死亡的重要原因之一^[3]。因此,分析新生儿肺动脉高压的危险因素,及时准确处理,是重要的临床工作。现回顾性分析南京医科大学第一附属医院儿科(即江苏省妇幼保健院新生儿病区)收治的41例肺动脉高压患儿病例。

1 对象和方法

1.1 对象

统计2017年1月—2019年12月南京医科大学第一附属医院儿科收治的肺动脉高压新生儿,分为足月儿组和早产儿组,其中,早产儿组23例,足月儿组18例。早产儿组男15例,女8例,胎龄为25⁺周~36⁺周,出生体重650~3 550 g[(1 930.44±782.83)g]。足月儿组男11例,女7例,胎龄为37⁺周~40⁺周,出生体重2 100~4 350 g[(3 127.78±637.97)g]。本研究经院伦理委员会批准,并知情同意。

1.2 方法

根据中华医学会儿科学分会的新生儿肺动脉高压诊断标准^[4],临床上新生儿出现无法改善的缺氧症状,血气分析显示持续性低氧血症($\text{PaO}_2 < 50 \text{ mmHg}$),伴或不伴有高碳酸血症($\text{PaCO}_2 > 50 \text{ mmHg}$),通过心脏彩超明确测定肺动脉收缩压,估测肺动脉收缩压 $> 30 \text{ mmHg}$ 。

对41例新生儿临床资料进行回顾性分析,收集新生儿主要原发疾病诊断、出生情况及母亲孕期情况等资料,分析影响新生儿肺动脉高压发生的危险因素。

1.3 统计学方法

应用SPSS 23.0软件进行统计分析。计数资料采用百分数(%)表示,组间比较采用 χ^2 检验,计量资料采用均数±标准差($\bar{x} \pm s$)表示。对新生儿肺动脉高压危险因素进行分析, $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 早产儿组与足月儿组基本情况及孕母情况单因素分析

回顾性分析了近3年共1 992例早产儿和3 394例足月儿,其中肺动脉高压早产儿23例(占1.15%);肺动脉高压足月儿18例(占0.53%)。2019年768例早产儿和1 302例足月儿中,肺动脉高压早产儿和肺动脉高压足月儿分别为12例(占1.5%)和13例(占0.99%)。肺动脉高压早产儿及足月儿合计41例,两组出生体重、胎龄的比较,差异有统计学意义($P < 0.05$)。两组孕母年龄、性别、分娩方式、双胎或多胎、Apgar评分比较,差异均无统计学意义($P > 0.05$)。早产儿组胎膜早破、胎盘早剥、绒毛膜羊膜炎、子痫的发生率高于足月儿组,差异有统计学意义($P < 0.05$)。足月儿组的孕母妊娠期糖尿病5例(占27.8%);早产儿组孕母妊娠期糖尿病1例(占4.3%),与足月儿组比较,差异有统计学意义($\chi^2 = 4.437, P = 0.035$)。

2.2 早产儿组与足月儿组危险因素分析的比较

早产儿组原发疾病以呼吸窘迫综合征为主(73.9%),容易合并肺出血(21.7%)、颅内出血(47.8%)。足月儿组原发疾病主要为先天性心脏病(室间隔缺损)(38.9%)。两组之间原发疾病及并发代谢性酸中毒、新生儿低血糖、气胸、败血症等统计分析见表1。

2.3 肺动脉高压新生儿基因测序结果与影像学检查结果

对部分肺动脉高压新生儿进行基因测序,有1例结果显示为22q11.21大片段DNA缺失(见图1A中红色标志区域为DNA缺失的区域),患儿表现为先天性心脏病(室间隔缺损),胸部CT示肺发育不良(图1B),支气管镜检查显示肺出血(图1C)。

2.4 早产儿组与足月儿组疗效与预后比较

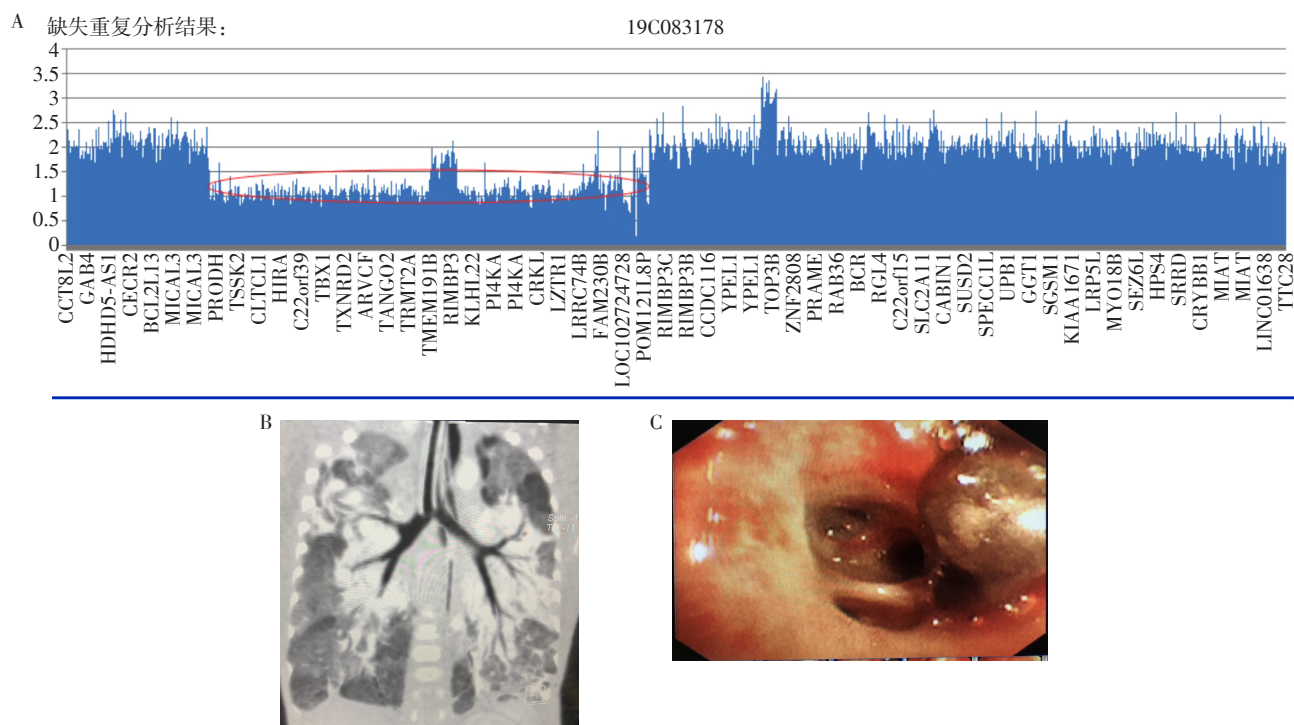
早产儿组与足月儿组分别有4例和1例使用了

表1 早产儿组和足月儿组原发疾病及并发症比较

Table 1 Comparison of primary diseases and complications between preterm and full-term groups [n(%)]

| 并发症 | 早产儿组 (n=23) | 足月儿组 (n=18) | χ^2 值 | P值 | 并发症 | 早产儿组 (n=23) | 足月儿组 (n=18) | χ^2 值 | P值 |
|-----------|----------------|----------------|------------|---------|----------|----------------|----------------|------------|-------|
| 呼吸窘迫综合征 | | | 19.158 | < 0.001 | 代谢性酸中毒 | | | 0.321 | 0.571 |
| 有 | 17(73.9) | 1(5.6) | | | 有 | 7(30.4) | 7(38.9) | | |
| 无 | 6(26.1) | 17(94.4) | | | 无 | 16(69.6) | 11(61.1) | | |
| 胎粪吸入综合征 | | | 2.687 | 0.101 | 新生儿败血症 | | | 0.589 | 0.443 |
| 有 | 0(0.0) | 2(11.1) | | | 有 | 13(56.5) | 8(44.4) | | |
| 无 | 23(100.0) | 16(88.9) | | | 无 | 10(43.5) | 10(55.6) | | |
| 新生儿肺炎 | | | 0.327 | 0.567 | 颅内出血 | | | 8.715 | 0.003 |
| 有 | 12(52.2) | 11(61.1) | | | 有 | 11(47.8) | 1(5.6) | | |
| 无 | 11(47.8) | 7(38.9) | | | 无 | 12(52.2) | 17(94.4) | | |
| 房间隔缺损 | | | 1.624 | 0.202 | 支气管肺发育不良 | | | 1.321 | 0.250 |
| 有 | 16(69.6) | 9(50.0) | | | 有 | 4(17.4) | 1(5.6) | | |
| 无 | 7(30.4) | 9(50.0) | | | 无 | 19(82.6) | 17(94.4) | | |
| 室间隔缺损 | | | 10.786 | 0.001 | 新生儿低血糖 | | | 0.319 | 0.572 |
| 有 | 0(0.0) | 7(38.9) | | | 有 | 4(17.4) | 2(11.1) | | |
| 无 | 23(100.0) | 11(61.1) | | | 无 | 19(82.6) | 16(88.9) | | |
| 动脉导管未闭 | | | 0.691 | 0.406 | 肺出血 | | | 4.433 | 0.035 |
| 有 | 18(78.3) | 12(66.7) | | | 有 | 6(21.7) | 1(5.6) | | |
| 无 | 5(21.7) | 6(33.3) | | | 无 | 12(78.3) | 17(94.4) | | |
| 其他先天性心脏病* | | | 1.513 | 0.219 | 气胸 | | | 0.802 | 0.370 |
| 有 | 6(26.1) | 8(44.4) | | | 有 | 1(4.3) | 0(0.0) | | |
| 无 | 17(73.9) | 10(55.6) | | | 无 | 22(95.7) | 18(100.0) | | |

*: 指除室间隔缺损、动脉导管未闭、房间隔缺损以外的先天性心脏病。



A: 基因测序; B: 胸部CT影像; C: 支气管镜检查结果。

图1 1例肺动脉高压新生儿的基因测序与影像学检查结果

Figure 1 A report of gene sequencing and CT image of a newborn with pulmonary hypertension

高频机械通气治疗,分别有8例和6例使用了西地那非治疗。足月儿组有1例使用了曲前列地尔,有1例使用了体外膜肺氧合(extracorporeal membrane oxygenation, ECMO)后死亡。早产儿组治愈21例,死亡2例,足月儿组治愈15例,死亡3例,治疗效果两组比较差异无统计学意义($P > 0.05$)。

3 讨论

本研究显示新生儿呼吸窘迫综合征是早产儿肺动脉高压的首要原发病。资料表明,呼吸窘迫综合征早产儿常常存在肺血管和肺实质发育差,肺泡表面活性物质不足,肺换气功能差,造成代谢性酸中毒和低氧血症,肺动脉痉挛,最终形成肺动脉压力明显增高^[5]。

本研究发现肺动脉高压的足月儿和早产儿都有一定比例的肺炎患儿,与国外报道一致^[6-7]。一般认为,由于细菌或内毒素引起心脏收缩功能受到抑制,血液黏滞度增高,肺微血管栓塞,同时应激情况下释放5-羟色胺等化学物质,促使肺血管持续痉挛,导致肺动脉高压的发生。

本研究显示肺动脉高压足月儿,室间隔缺损的发病率较高,肺动脉高压早产儿发生动脉导管未闭、房间隔缺损的比例较高,这与国内外研究相一致^[8-9]。室间隔缺损和动脉导管未闭引起血液分流,使肺循环血流增多,阻力增加,心肌不能持续耐受压力负荷,容易发生右心衰,造成缺氧进一步加重,肺动脉压力持续性增高。

本研究发现,早产儿组母亲妊娠并发症比例高于足月儿组,主要包括胎膜早破、胎盘早剥、子痫等。资料表现,母亲妊娠期并发症对新生儿肺动脉高压的发生有显著影响。这些并发症造成宫内应激和慢性缺氧,造成血流动力学改变,影响到肺动脉循环负荷和血管本身的发育^[4,10-11]。

本研究的一个有意义的发现,是1例肺动脉高压新生儿的基因测序报告显示其存在22q11.21拷贝数片段的缺失。该病为常染色体显性遗传性疾病,临床表现可以包括肺动脉瓣狭窄、室间隔缺损、法洛氏四联症,甚至圆锥动脉干畸形,可伴有肌张力、听力、语言能力的下降,及智力残疾。类似的国外文献显示,存活的患儿肺动脉高压进展可以越来越严重,甚至死于肺动脉高压^[12]。

本研究与其他研究不一致的是足月儿胎粪吸入发生率不高,肺动脉高压足月儿组与早产儿组比较差异也无统计学意义,这可能与样本量较小有

关。新生儿胎粪吸入综合征是吸入性肺炎的一种,当胎儿因宫内窘迫或分娩时窒息等原因引起胎粪吸入气道,造成机械性梗阻和缺氧,从而导致肺动脉痉挛和肺动脉平滑肌变厚,产生肺动脉高压^[13-14]。尽管本研究中的胎粪吸入发生率较低,但其中1例患儿病情极其危重,肺动脉高压值高达120 mmHg,先后给予西地那非、高频机械通气、NO吸入等措施,最终抢救成功。

综上,本研究通过回顾性分析了新生儿肺动脉高压的临床资料,发现早产儿发生肺动脉高压的高危原发病是呼吸窘迫综合征、重症肺炎、肺出血和孕母有胎膜早破、胎盘早剥等并发症。患有先天性心脏病如房间隔缺损的足月儿,要重视肺动脉高压的及时诊断和及早处理。

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