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Genetic Contribution to Patent Ductus Arteriosus in the Premature Newborn

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Abstract

BACKGROUND—The most common congenital heart disease in the newborn population, patent ductus arteriosus, accounts for significant morbidity in preterm newborns. In addition to prematurity and environmental factors, we hypothesized that genetic factors play a significant role in this condition.

OBJECTIVE—The objective of this study was to quantify the contribution of genetic factors to the variance in liability for patent ductus arteriosus in premature newborns.

PATIENTS AND METHODS—A retrospective study (1991–2006) from 2 centers was performed by using zygosity data from premature twins born at ≤36 weeks' gestational age and surviving beyond 36 weeks' postmenstrual age. Patent ductus arteriosus was diagnosed by echocardiography at each center. Mixed-effects logistic regression was used to assess the effect of specific covariates. Latent variable probit modeling was then performed to estimate the heritability of patent ductus arteriosus, and mixed-effects probit modeling was used to quantify the genetic component.

RESULTS—We obtained data from 333 dizygotic twin pairs and 99 monozygotic twin pairs from 2 centers (Yale University and University of Connecticut). Data on chorioamnionitis, antenatal steroids, gestational age, body weight, gender, respiratory distress syndrome, patent ductus arteriosus, necrotizing enterocolitis, oxygen supplementation, and bronchopulmonary

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dysplasia were comparable between monozygotic and dizygotic twins. We found that gestational age, respiratory distress syndrome, and institution were significant covariates for patent ductus arteriosus. After controlling for specific covariates, genetic factors or the shared environment accounted for 76.1% of the variance in liability for patent ductus arteriosus.

CONCLUSIONS—Preterm patent ductus arteriosus is highly familial (contributed to by genetic and environmental factors), with the effect being mainly environmental, after controlling for known confounders.

Keywords

neonate; patent ductus arteriosus; twins; genetic

With increasing survival of premature newborns, patent ductus arteriosus (PDA) has become the most common form of congenital heart disease in the newborn period.[1] The incidence of PDA in very low birth weight (<1500 g) newborns is 37%[2] and 42% among those born at <1000 g.[3] The major factors believed to influence patency of the ductus arteriosus include prematurity and the presence of respiratory distress syndrome (RDS).[1] PDA is a significant independent risk factor for necrotizing enterocolitis (NEC),[4] bronchopulmonary dysplasia (BPD),[5,6] and cerebral palsy.[7] Although the diagnosis of PDA using echocardiography has become routine, there is considerable controversy regarding the appropriate management of this condition.[8-14] Despite significant progress in the diagnosis and management options for PDA, it remains a major contributor to neonatal morbidity and mortality.[15,16]

A better understanding of the pathogenesis would be useful for devising specific strategies to treat PDA and to thereby improve newborn morbidity. We hypothesized that, in addition to prematurity and environmental factors, there is a susceptibility conferred by genetic factors. The goal of this study was to quantify the contribution of these unknown genetic factors by analyzing preterm monozygotic twin pairs who share 100% of their chromosome-encoded genes with dizygotic twin pairs who, on average, share 50%.

PATIENTS AND METHODS

Subjects

Data on premature twins surviving to hospital discharge, born at ≤36 weeks' gestation from January 1, 1991, to December 31, 2006, were collected from 2 centers: the University of Connecticut and Yale University. The institutional review boards of each participating center approved the contribution of data to this study.

Definitions

The zygosity of each twin pair was determined by histopathologic examination of the placenta, with additional confirmation using gender concordance or discordance. Information about histologic chorioamnionitis and the use of antenatal steroids was obtained from the maternal charts. PDA was diagnosed via echocardiography by pediatric cardiologists at each site.[17] Requests for the diagnosis of PDA were made by the attending neonatologist based on clinical suspicion of a symptomatic PDA. Data were not available on the grading/severity of the shunt. RDS was defined as the presence of respiratory distress with an oxygen requirement in the first 6 hours of life, accompanied by a characteristic chest radiograph. Duration of oxygen use was defined as the total number of days that the newborn required the use of supplemental oxygen while hospitalized (>21%). NEC was defined as stage 2 or more as per modified Bells' criteria.[18] BPD was defined as the need for supplemental oxygen at 36 weeks' postmenstrual age in association with characteristic radiographic changes.[18]

Statistical Analyses

Demographic data were analyzed using the Student's *t* test or χ^2 analysis, where appropriate. To assess the independence of the twins in a pair, the PDA rate was calculated as the number of affected twins divided by the total number of twins. The expected concordance under the assumption that the twins are independent was the probability of both twins in a pair having a PDA and was calculated as $\{(rate)^2\}$. The number of expected concordant twin pairs was calculated as $\{n(rate)^2\}$ where *n* refers to the total number of twin pairs in the monozygotic and dizygotic groups. The observed concordance was the actual PDA concordance between the twins in a pair. Observed to expected concordance was compared using χ^2 analysis.

To calculate the heritability of susceptibility to PDA, we used the formula $2(C_{MZ} - C_{DZ})$, where C_{MZ} is the concordance rate for monozygotic twins and C_{DZ} is the concordance rate for dizygotic twins, as reported previously.[18] To test whether there is an excess of concordance in monozygotic twins, we calculated the average rate of concordance in both monozygotic and dizygotic twins. Then, the observed concordance was compared with the expected concordance in a χ^2 test.

Mixed-effects logistic regression (MELR) analysis was performed to identify the impact of putative risk factors on PDA. The covariates used in the model included male gender, gestational age (GA), birth weight (BW), RDS, duration of supplemental oxygen use, and treating institution (INST). The parameter estimates were based on the observations without missing data. The status of the outcomes from twin pairs was treated as a correlated event. INST was evaluated as an overall variable, as well as one institution compared with the other, a reference institution, chosen at random. An MELR model was fitted to assess the relationship between the covariates listed and the outcome of interest (PDA) and to incorporate the correlation between twin pairs.

Latent variable probit modeling for twin data was then used to estimate the variance in liability for PDA. A mixed-effects probit model was fitted to estimate the genetic contribution to PDA by adjusting for all of the significant covariates used in the MELR analysis. A liability variable was estimated underlying the respective outcome. This variable was assumed to follow a normal distribution with the mean dependent on the MELR covariates. The variance was partitioned into a genetic component, a shared nongenetic component, and a random component. The sum of the first 2 components constituted the overall sharing between twins and was determined from the correlation between monozygotic twins and dizygotic twins. We estimated the heritability (ie, the ratio of the genetic variance to the total variance in liability) based on a model that assumed that the correlation among twins resulted from both a genetic and nongenetic component.

Anonymous clinical data, formatted in Excel spread-sheets (Microsoft, Redmond, WA), were forwarded from each institution to the statistical core at Yale University. Statistical analyses were performed by using SAS 9.1 (PROC GLIMMIX and PROC NLMIXED [SAS Institute, Inc, Cary, NC) and Mx.[19] A *P* value of <.05 was considered statistically significant.

RESULTS

PDA was diagnosed in 134 (15.5%) of 864 newborns from our cohort. The incidence of PDA was inversely proportional to BW, with the majority of disease occurring in the population <1000 g. In these newborns, 67 (49%) of 136 were diagnosed with PDA as compared with 40 (20%) of 197 in those with BW 1000 to 1500 g and 17 (6.5%) of 310

newborns with BW 1501 to 2000 g. We also noted that only 10 (4.5%) of 221 newborns were diagnosed in the subpopulation with BW >2000 g (Table 1).

Zygosity data composed of 99 monozygotic and 333 dizygotic twin pairs from the 2 institutions were used for analysis. The 432 twin pairs had a mean GA and BW of 31.1 weeks and 1637.7 g, respectively. Despite a discrepancy in the overall number of twin pairs in each group, no statistically significant differences were observed between monozygotic and dizygotic twins with respect to maternal chorioamnionitis; exposure to antenatal steroids; GA; BW; gender; 5-minute Apgar score; the incidences of RDS, BPD, and NEC; and duration of supplemental oxygen use (Table 2).

We initially performed an unadjusted concordance analysis to identify whether a genetic effect exists for PDA in our premature newborn population. Tables 3 and 4 shows that the concordance rate of twins was significantly higher, if the twins are assumed independent ($P < .0001$). The concordance rate of monozygotic twins was higher than that in dizygotic twins, but the difference was not statistically significant ($P = .34$).

Next, MELR analysis was performed using PDA as the dependent variable in an attempt to identify significant covariates in our cohort that may have contributed to the outcome of interest. The analysis determined RDS (odds ratio [OR]: 4.753 [95% confidence interval (CI): 2.303–9.811]; $P < .001$), lower GA (OR: 0.805 [95% CI: 0.666 – 0.973]; $P = .025$), and INST (OR: 9.905 [95% CI: 4.470–21.947]; $P < .001$) to be significant predictors for PDA (Table 5).

Although BW seems only marginally significant from this analysis, we found that a model that includes BW, RDS, and INST fit significantly better than a model that did not include BW. Once significant nongenetic cofactors for PDA were identified by the MELR analysis, a latent variable probit model was used to estimate the genetic susceptibility to PDA. Our model assumed that genetic and shared and unshared nongenetic factors contributed to the correlation among twins. Using this model, we determined that 76.1% (95% CI: 62.5%–89.8%; $P < .001$) of the variance in liability to PDA was the result of genetic factors or the shared environment. There is some evidence for the contribution of genetic factors alone of 12.3% (95% CI: 0%–98%, $P = .779$), but the estimate is not statistically significant. This is consistent with the results in Tables 3 and 4.

DISCUSSION

In normal fetal life, ductus arteriosus patency is maintained by low fetal systemic arterial oxygen tension and prostaglandins.[20] In term newborns, the ductus usually closes within 48 hours after birth concurrent with a rise in systemic vascular resistance and oxygen tension, a drop in pulmonary vascular resistance, and decreased circulating prostaglandins that characterize the physiologic shifts from fetal circulation. Until recently, PDA, which accounts for 2% to 7% of congenital heart disease in term newborns, was not considered a genetic disease. [21] Recent studies, however, implicate specific genes that contribute to congenital heart defects,[22] including PDA. For example, mutations in the transcription factor TFAP2B are responsible for Char syndrome, a rare autosomal dominant syndromic form of PDA.[23] Although a candidate gene has not yet been proposed for a nonsyndromic form of PDA, a genome-wide linkage analysis of 21 unrelated consanguineous PDA case subjects from Iran identified a single locus, PDA1, on 12q24.[21]

PDA is more common in preterm newborns. A multitude of factors, such as excess sensitivity to prostaglandins and nitric oxide, response to inflammatory mediators, and relative resistance to local hypoxia-ischemia, are implicated in patency of the ductus arteriosus in the preterm newborn.[20] Cyclooxygenases, a class of enzymes that regulate the

production of prostaglandins, affect patency in animal studies.[24,25] Other studies revealed the role of oxygen-sensitive potassium channels and ρ-kinase activation in functional closure.[26,27]

In a candidate gene study of 141 low BW newborns, Derzbach et al[28] reported that boys with the "p" allele of the estrogen receptor-α gene PvuII pP polymorphism were at lower risk for PDA but with a wide CI (OR: 0.24 [95% CI: 0.05–0.97]). In another candidate gene study of 153 low BW newborns, Bokodi et al[29] showed by stepwise logistic regression analysis that carriers of the interferon γ (+874) T allele were protected against PDA (OR: 0.43 [95% CI: 0.19–0.97]) with a similarly wide CI. Although these small studies offer tantalizing clues to a genetic predisposition toward PDA, ours is the first study that formally isolated and quantified the overall heritability.

The statistical model took into consideration known and unknown nongenetic factors. Unknown factors included the potential influences of race and neonatal sepsis, in addition to other, unidentified factors. We calculated the rate of PDA and the expected concordance rates (Tables 3 and 4) under different assumptions (1 and 2) to test the null hypothesis that concordances between monozygotic and dizygotic twins are the same. In assumption 1, the contribution to PDA from nongenetic factors is independent for each infant, regardless of shared (within a twin pair) or nonshared (between twin pairs) environment. In assumption 2, the contribution to PDA from nongenetic factors is the same for each twin pair. The hypothesis with assumption 1 was rejected ($P < .0001$), whereas the hypothesis with assumption 2 was not rejected ($P = .34$). By modeling the effects of these nongenetic components, we estimated that 12.3% of the variance in liability to PDA was attributable to genetic factors alone.

We used similar models to quantify the genetic heritability to BPD (53%)[18] and retinopathy of prematurity (70%)[30] in preterm newborns. Other investigators used similar twin models to estimate the heritability of several cardiovascular disorders, including exercise behavior and respiratory sinus arrhythmia (84%–88%),[31] hypertension (44%–66%),[32,33] coronary artery disease (34%),[33] and death from coronary artery disease (38%–57%).[34]

Although prophylactic indomethacin for intraventricular hemorrhage prophylaxis was used only at Yale University for infants with BWs of <1250 g, there were no institutional policy differences in the use of antenatal steroids. The use of antenatal steroids in our cohort reflects the customarily low use in the early 1990s, and the formal American College of Obstetrics and Gynecology recommendations that it not be used in infants at ≥34 weeks (>32 weeks, if membranes were ruptured) of gestation.[35,36] The use of antenatal steroids in our cohort did not affect the results, because, as shown in Table 2, there was no statistically significant difference in exposure between monozygotic and dizygotic twins. It is, however, important to note that institutional differences were identified in the multiple-effects regression analysis (as shown in Table 5) and controlled for in our subsequent analyses.

Some limitations exist with our data set. As mentioned in the Methods section, at both institutions, requests for the diagnosis of PDA were made by the attending neonatologist based on clinical suspicion of a symptomatic PDA. We only used echocardiographic evidence of PDA, done by pediatric cardiologists, to be included in the study. We did not have information on the time of diagnosis of the PDA in our database. The inclusion of PDA was not based on the need for treatment. Because the request for an echocardiogram was made by the attending neonatologist based on his/her clinical suspicion, there was a potential for selection bias. By design, our cohort was restricted to twin pairs with available zygosity information and was, therefore, limited in numbers. We included most of the known potential contributing factors to PDA, but not all. We did, however, attempt to

control for these unknown variables in our statistical model. Furthermore, the retrospective nature precluded DNA confirmation of zygosity. Placental histopathology and gender were instead used to determine zygosity status. A monochorionic placenta was regarded as representing monozygotic twins.[37] Approximately 9% of similar gender dichorionic placentas are monozygotic.[38] On the other hand, in rare instances, dizygotic twins may have a monochorionic placenta.[37] The validity of our results was not affected when adjustments were made for these potential misclassifications using worst-case scenarios.

CONCLUSIONS

As with the term PDA, which traditionally was considered a sporadic disease,[21] these data show that preterm PDA is highly familial (genetic plus environmental factors). Although the effect was mainly environmental, the magnitude of genetic contribution warrants additional investigation. We hope that these novel findings will serve as an impetus to the identification of specific candidate genes for this condition. Because preterm PDA and the treatment protocols used to close it lead to significant morbidity and mortality, knowledge of the genes responsible for maintaining the balance between patency and closure is an important step toward developing pharmacogenetic strategies tailored to individual genomes.

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Abbreviations

PDA	patent ductus arteriosus
RDS	respiratory distress syndrome
NEC	necrotizing enterocolitis
BPD	bronchopulmonary dysplasia
MELR	mixed-effects logistic regression
GA	gestational age
BW	birth weight
INST	treating institution
OR	odds ratio
CI	confidence interval

What's Known on This Subject

PDA in preterm neonates is a common cause of morbidity, but the quantification of genetic and environmental factors contributing to it is not known.

What This Study Adds

Preterm PDA is contributed to by genetic and environmental factors, with the effect being mainly environmental.

TABLE 1

Incidence of PDA According to BW

BW, g	Incidence of PDA, *n/N* (%)
<1000	67/136 (49.0)
1000–1500	40/197 (20.0)
1501–2000	17/310 (6.5)
>2000	10/221 (4.5)

TABLE 2

Comparison of Demographic Data for Monozygotic and Dizygotic Twin Pairs

Variable	Monozygotic (*n* = 198)	Dizygotic (*n* = 666)	*P*
Histologic chorioamnionitis, *n* (%)	7/178 (4)	33/566 (6)	.328
Antenatal steroids, *n* (%)	68/184 (37)	104/608 (17)	.467
GA, mean ± SD, wk	30.3 ± 2.78	30.1 ± 3.01	.350
BW, mean ± SD, g	1622 ± 551	1642 ± 553	.646
Male gender, *n* (%)	97 (49)	351 (53)	.359
Apgar score at 5 min, median ± SD	8.15 ± 1.23	8.18 ± 1.29	.718
RDS, *n* (%)	101 (51)	312 (47)	.303
BPD, *n* (%)	38 (19)	112 (17)	.439
NEC, *n* (%)	6 (3)	41 (6)	.089
PDA, *n* (%)	36 (18)	98 (15)	.237
Supplemental oxygen, mean ± SD, d	17.9 ± 26.9	16.2 ± 30.0	.473

TABLE 3

PDA According to Zygosity

Variable	Twin Pairs, *n*	One With PDA, *n*	Both With PDA, *n*
Monozygotic	99	10	13
Dizygotic	333	34	32

TABLE 4

Testing Independence and Concordance of the Twins

Variable	Expected Concordance	Observed Concordance	*P*
Independence			<.001
Monozygotic	2.378[a]	13	
Dizygotic	8.000[a]	32	
Excess of concordance of the monozygotic twins			.34
Monozygotic	10.3[b]	13	
Dizygotic	34.6[b]	32	

[a]The expected concordance was calculated under the assumption that twins are independent, the rate of PDA is [10 + (2 × 13) + 34 + (2 × 32)]/864 = 0.155, and the expected concordance for PDA is $99(0.155)^2$ for monozygotic twins and $333(0.155)^2$ for dizygotic twins.

[b]The expected concordance was calculated under the assumption that the monozygotic and dizygotic twins have the same level of concordance that is estimated by (13 + 32)/432 = 0.104, and the expected concordance for PDA is 99 × 0.104 for monozygotic twins and 333 × 0.104 for dizygotic twins.

TABLE 5

MELR Analysis for PDA

Variable	OR	95% CI	*P*
Male gender	0.802	0.475–1.356	.407
GA	0.805	0.666–0.973	.025
BW	0.999	0.998–1.000	.099
RDS	4.753	2.303–9.811	<.001
INST (University of Connecticut)	9.905	4.470–21.947	<.001