

OBSTETRICS

Association of cord blood digitalis-like factor and necrotizing enterocolitis

Steven W. Graves, PhD; Michael S. Esplin, MD; Paula McGee, PhD; Dwight J. Rouse, MD; Kenneth J. Leveno, MD; Brian M. Mercer, MD; Jay D. Iams, MD; Ronald J. Wapner, MD; Yoram Sorokin, MD; John M. Thorp, MD; Susan M. Ramin, MD; Fergal D. Malone, MD; Mary J. O'Sullivan, MD; Alan M. Peaceman, MD; Gary D. V. Hankins, MD; Donald J. Dudley, MD; Steven N. Caritis, MD; for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network

OBJECTIVE: Endogenous digoxin-like factor (EDLF) has been linked to vasoconstriction, altered membrane transport, and apoptosis. Our objective was to determine whether increased EDLF in the cord sera of preterm infants was associated with an increased incidence of necrotizing enterocolitis (NEC).

STUDY DESIGN: Cord sera from pregnant women enrolled in a randomized trial of MgSO₄ for fetal neuroprotection were analyzed for EDLF using a red cell Rb⁺ uptake assay in which the inhibition of sodium pump-mediated Rb⁺ transport was used as a functional assay of EDLF. Specimens were assayed blinded to neonatal outcome. Cases (NEC, n = 25) and controls (neonates not developing stage 2 or 3 NEC, n = 24) were matched by study center and gestational age. None of the women had preeclampsia. Cases and controls were compared using the Wilcoxon test for continuous

and the Fisher exact test for categorical variables. A conditional logistic regression analysis was used to assess the odds of case vs control by EDLF level.

RESULTS: Cases and controls were not significantly different for gestational age, race, maternal steroid use, premature rupture of membranes, or MgSO₄ treatment. In logistic models adjusted for treatment group, race, premature rupture of membranes, and gestational age, cord sera EDLF was significantly associated with development of NEC ($P = .023$).

CONCLUSION: These data demonstrated an association between cord sera EDLF and NEC.

Key words: cord blood, digitalis-like factor, necrotizing enterocolitis, pregnancy, sodium pump

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From the Department of Chemistry and Biochemistry, Brigham Young University, Provo, (Dr Graves), and the Departments of Obstetrics and Gynecology, Utah Health Science Center, Salt Lake City (Dr Esplin), UT; University of Alabama at Birmingham School of Medicine, Birmingham, AL (Dr Rouse); University of Texas Southwestern Medical Center, Dallas (Dr Leveno), University of Texas Health Science Center at Houston—Children's Memorial Hermann Hospital, Houston (Dr Ramin), University of Texas Medical Branch, Galveston (Dr Hankins), and University of Texas at San Antonio School of Medicine, San Antonio (Dr Dudley), TX; Case Western Reserve University—MetroHealth Medical Center, Cleveland, OH, and University of Tennessee, Memphis, TN (Dr Mercer); The Ohio State University College of Medicine, Columbus, OH (Dr Iams); College of Physicians and Surgeons, Columbia University, New York, NY (Dr Malone); Jefferson Medical College, Thomas Jefferson University, and Drexel University College of Medicine, Philadelphia (Dr Wapner), and University of Pittsburgh School of Medicine, Pittsburgh (Dr Caritis), PA; Wayne State University School of Medicine, Detroit, MI (Dr Sorokin); University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC (Dr Thorp); Miller School of Medicine, University of Miami, Miami, FL (Dr O'Sullivan); Feinberg School of Medicine, Northwestern University, Chicago, IL (Dr Peaceman); and the Biostatistics Center, George Washington University, Washington, DC (Dr McGee). Dr Rouse is currently at the Warren Alpert Medical School of Brown University. Dr Wapner is currently at Columbia University Medical Center. Additional Maternal-Fetal Medicine Units Network participants are listed in the Acknowledgments.

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Reprints: Steven W. Graves, PhD, Department of Chemistry and Biochemistry, BNSN C212, Brigham Young University, Provo, UT 84602. swgraves@chem.byu.edu.

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Early, preterm deliveries result in infants at risk for major medical complications and death.^{1,2} Among the most serious problems is necrotizing enterocolitis (NEC), which represents a leading cause of neonatal mortality and morbidity.^{3,4} NEC can be characterized by biochemical and morphological changes, but the primary cause for this disease is poorly understood and the immediate mechanisms involved are not fully worked out. The incidence is inversely related to gestational age and birthweight.¹

NEC is characterized by one or more of the following: reduced bowel motility, bacterial infection, a marked inflammatory response perhaps representing activation of toll-like receptor 4, or difficulty in digestion (especially synthetic infant formula), which results in necrosis of a portion of the intestine.⁵⁻⁷ It often occurs suddenly and progresses rapidly and can prove lethal. In severe cases, surgical resection of the bowel is required, and this may result in long-term complications, including neurodevelopmental deficits.^{5,6}

Endogenously produced inhibitors of the sodium pump have been implicated in a number of diseases, especially hypertensive disorders.⁸⁻¹⁰ It is also well documented that the endogenous digitalis-like factors (EDLFs) are present in the placenta,¹¹⁻¹³ cord serum,¹⁴ and neonatal blood.^{14,15} There is evidence that levels of these factors are proportionately higher in the neonatal circulation and cord blood the more premature the delivery.^{14,15} The EDLFs by definition block ion transport and consequently nutrient transport coupled to the sodium pump but can also cause apoptosis of exposed cells in a cell type and dose dependent manner.¹⁶⁻¹⁸ Moreover, there is preliminary evidence that some complications of prematurity are reduced in response to antibody Fab treatment that targets EDLFs in the maternal circulation just prior to delivery.¹⁹ Thus, we hypothesized that EDLFs may participate in NEC and that higher EDLF levels are associated with a higher incidence of NEC.

MATERIALS AND METHODS

Patient population

Cord sera were obtained as part of a previously completed study, the Beneficial Effects of Antenatal Magnesium Sulfate Trial carried out under the auspices of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. This multicenter trial tested whether prophylactic magnesium sulfate given to women, for whom preterm delivery was imminent, reduced the risk of death or moderate to severe cerebral palsy in their children.²⁰

The study enrolled pregnant women presenting from 24.0 to 31.6 weeks' gestation with advanced preterm labor, premature rupture of the membranes (pPROM), or indicated deliveries. Women were randomized to receive either intravenous magnesium sulfate or placebo.

Cord sera analyzed in this nested case-control study were selected by the Maternal-Fetal Medicine Units (MFMU) Network's independent Biostatistics Center at George Washington University

to produce a set of specimens matched for maternal characteristics. Specimens included cord sera from 28 neonate cases with NEC and 27 matched controls (by center and gestational age) selected for further analysis.

Gestational age categories were the following: 24-26 weeks, 27-29 weeks, and 30-32 weeks. Cases were identified as women with a singleton pregnancy delivering prior to 32 weeks' gestation, during which the neonate experienced stage 2 or 3 NEC. Controls were mothers with the same characteristics but during which the neonate was live born, survived to hospital discharge, and experienced no bronchopulmonary dysplasia, severe necrotizing enterocolitis, or intraventricular hemorrhage (IVH) grades III or IV. Serum volume was sufficient to allow EDLF levels to be obtained on 25 of the controls and 24 of the cases. Subjects with EDLF values between 0% and 2% were reassigned a value of zero. Baseline characteristics are presented in Table 1. None of the selected subjects had preeclampsia. Researchers analyzing these

TABLE 1
Maternal characteristics

Characteristic	Controls (n = 24)	NEC cases (n = 25)	P value
Race			
African American	13 (54%)	12 (48%)	1.0
Hispanic	3 (12.5%)	4 (16%)	
Caucasian	8 (33%)	9 (36%)	
Labor type			
Spontaneous	13 (54%)	16 (64%)	.45
Induced	7 (29%)	3 (12%)	
No labor	2 (8%)	2 (8%)	
Spontaneous, augmented	2 (8%)	4 (16%)	
Preeclampsia	0 (0%)	0 (0%)	n/a
Any maternal steroid use	24 (100%)	25 (100%)	n/a
pPROM	23 (96%)	21 (84%)	.35
Active treatment group, MgSO ₄	11 (46%)	13 (52%)	.78
Gestational age at delivery, wks	28 ± 2	28 ± 2	.66

Results are presented as means ± SD or n (%).

n/a, not applicable; NEC, necrotizing enterocolitis; pPROM, premature rupture of membranes.

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