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Original Article

Antecedents of Perinatal Cerebral White Matter Damage With and Without Intraventricular Hemorrhage in Very Preterm Newborns

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ABSTRACT

BACKGROUND: Isolated periventricular leukomalacia, defined as periventricular leukomalacia unaccompanied by intraventricular hemorrhage, is reportedly increased in newborns with systemic hypotension and in infants who received treatment for systemic hypotension or a patent ductus arteriosus. **METHODS:** This study sought to determine if the risk profile of one or more hypoechoic lesions unaccompanied by intraventricular hemorrhage, our surrogate for isolated periventricular leukomalacia, differs from that of one or more hypoechoic lesions preceded or accompanied by intraventricular hemorrhage. We compared extremely preterm infants (i.e., gestation 23-27 weeks) with each of these entities to 885 extremely preterm infants who had neither an isolated hypoechoic lesion nor a hypoechoic lesion preceded or accompanied by intraventricular hemorrhage. **RESULTS:** The risk of a hypoechoic lesion with intraventricular hemorrhage (N = 61) was associated with gestation <25 weeks, high Score for Acute Neonatal Physiology, early recurrent or prolonged acidemia, analgesic exposure, and mechanical ventilation 1 week after birth. **CONCLUSIONS:** In this large, multicenter sample of extremely low gestational age newborns, the risk profile of a hypoechoic lesion unaccompanied by intraventricular hemorrhage differed from that of a hypoechoic lesion with intraventricular hemorrhage. This suggests that hypoechoic lesions accompanied or preceded by intraventricular hemorrhage (our surrogate for periventricular hemorrhagic infarction) may have a different causal pathway than hypoechoic lesions without intraventricular hemorrhage, our surrogate for periventricular leukomalacia.

Introduction

In a recently published report, the risk of isolated periventricular leukomalacia (PVL), defined as PVL unaccompanied by intraventricular hemorrhage (IVH), was increased if the newborn had systemic hypotension or received treatment for systemic hypotension or patent ductus arteriosus (PDA) [1]. Our study sought to determine if the risk profile of a hypoechoic lesion unaccompanied by IVH (the surrogate for isolated PVL) differs from

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Table 1. Ultrasound findings of children with hypoechoic lesions with or without IVH (column percents)

Ultrasound Lesion	Hypoechoic Lesion		Total
	With IVH	Without IVH	
Ventriculomegaly	72	15	50
Diagnoses			
PVHI	77	5	49
PVL	39	61	49
Hemorrhage			
Only 1 lateral ventricle	13	-	8
Hyperechoic lesions			
Unilateral	52	17	39
4+ Unilateral boxes*	26	7	19
7+ Bilateral boxes*	18	5	13
Hypoechoic lesions			
Unilateral	64	41	56
4+ Unilateral boxes*	16	2	11
7+ Bilateral boxes*	3	15	8
Maximum column N	61	41	102

Abbreviations:
IVH = Intraventricular hemorrhage
PVHI = Periventricular hemorrhagic infarction
PVL = Periventricular leukomalacia

* The data collection forms required that information about hyperechoic and hypoechoic lesions be recorded for every one of 16 white matter zones in each cerebral hemisphere on coronal imaging. These anatomic zones are represented by boxes on the data collection form.

that of a hypoechoic lesion accompanied or preceded by IVH.

Half of extremely low gestational age newborn (ELGAN) infants who developed hypoechoic lesions (known as echolucency in prior published reports) in the periventricular cerebral white matter on a brain ultrasound scan had blood in a lateral ventricle (IVH) on a previous ultrasound scan [2].

The frequent coexistence of hypoechoic lesions and IVH raises questions about how they might be related. One possibility is that a common vulnerability, such as the immaturity of the developing brain and its blood vessels, increases the risk of both IVH and hypoechoic lesions.

Another possibility is that IVH, which may occur earlier than hypoechoic lesions, contributes to the risk of white matter damage. For example, some periventricular hyperechoic lesions that accompany large IVH are attributed to infarction that follows compression of veins by a distended ventricle [3]. This explanation does not account for large periventricular hyperechoic lesions that are not accompanied by a blood-distended ventricle [4,5].

A third explanation hypothesizes that blood components toxic to white matter move across the ventricular ependyma and injure immature oligodendrocytes and other vulnerable brain cells [4]. This explanation could also account for the diffuse white matter damage that is evident as white matter volume loss and subsequently as ventriculomegaly.

White matter damage, however, is not always preceded by or associated with IVH, suggesting that other etiologic factors might play a role. In a recent study that compared 20 very low birth weight infants who were diagnosed with PVL not preceded or accompanied by IVH to 98 very low birth weight infants who had no cranial ultrasound abnormality, “isolated PVL” was associated with low birth weight, hypotension requiring inotropic therapy and surgical closure of a hemodynamically significant PDA beyond age 7 days [1].

Our study describes an analysis of etiologic factors for hypoechoic lesions (without IVH) in a large cohort of extremely preterm infants enrolled in the ELGAN study. In this study, every scan identified as having a hypoechoic lesion was read by other sonologists until consensus was achieved on the presence or absence of this characteristic [6]. Sonologists were also given the opportunity to offer a diagnosis of either PVL or periventricular hemorrhagic infarction (PVHI); however, consensus for these diagnoses was not sought [7]. Thus, whereas we are confident about classifying scans by the presence or absence of hypoechoic lesions, our surrogate for PVL, we are less confident about the classification of PVL or PVHI.

These analyses tested hypotheses about the antecedents of isolated hypoechoic lesions as a surrogate for PVL [1]. The term *isolated*, in this context, signifies the absence of IVH and is not intended to signify a singular hypoechoic lesion. Specifically, the study compared the antecedents or correlates of hypoechoic lesions in the cerebral white matter of very preterm newborns who did not have IVH with those who had both a hypoechoic lesion and IVH and with those who had neither a hypoechoic lesion nor IVH.

Methods

The ELGAN study

The ELGAN study was designed to identify characteristics and exposures that increase the risk of structural and functional neurological disorders in children born before 28 weeks’ gestation. The study enrolled 1249 mothers and their 1506 infants born before 28 weeks’ gestation at one of 14 participating institutions between 2002 and 2004 [8]. The study was approved by the institutional review boards at each site. For this report, we limited the sample to the 987 infants who had two protocol cranial ultrasound scans after postnatal day 5 [Table 1].

Demographic and pregnancy variables

After delivery, a trained research nurse interviewed each mother in her native language, using a structured data collection form that was outlined in a procedural manual prior to the start of the study. For characteristics, exposures, and events prior to admission, reliance was placed on the mother’s report, even when her medical record provided discrepant information.

Shortly after the mother’s discharge, the research nurse reviewed the maternal chart using a second structured data collection form. The medical record was relied on for events following admission.

The clinical circumstances that led to preterm delivery were operationally defined using both data from the maternal interview and data abstracted from the medical record [9]. Each mother–infant pair was assigned to the category that best described the primary reason for the preterm delivery.

Protocol ultrasound scans

Routine ultrasound scans were performed by technicians at each of the participating hospitals using high-frequency transducers (7.5 and 10 MHz). Ultrasound studies always included six standard quasi-coronal views and five sagittal views using the anterior fontanel as the sonographic window. Protocol 1 scans were obtained between day 1 and day 4; protocol 2 scans were obtained between day 5 and day 14, and protocol 3 scans were obtained between day 15 and week 40.

Observer variability was minimized by the creation of a manual and data collection forms and by scheduled conference calls to discuss aspects of images prone to different interpretations [6]. All ultrasound scans were read by two independent sonologists who were not provided

Table 2. Characteristics of the mother and her pregnancy with children with hypoechoic lesions with or without IVH (column percents)

Maternal & Pregnancy Characteristics	Hypoechoic Lesion			Total
	Yes		No	
	IVH		IVH	
	Yes	No	No	
Maternal characteristics				
Racial identity				
White	53	53	59	565
Black	32	33	27	270
Hispanic				
Yes	16	17	13	131
Age				
<21	20	15	14	145
>35	15	12	19	178
Years of education				
≤12	39	54	45	427
≥16 (college)	25	14	32	262
Marital status				
Single	44	51	44	434
Self-support				
Yes	59	74	64	614
Public insurance				
Yes	39	56	42	406
Prepregnancy BMI				
<18.5	5	8	8	77
≥30	21	19	22	204
Pregnancy characteristics				
Years since last pregnancy				
<1	15	20	18	98
1 to <2	36	28	30	167
Smoking				
Yes	14	16	14	137
Assisted conception				
Yes	22	14	20	193
Vaginal bleeding				
≤12 weeks*	39	41	38	366
>12 weeks*	18	22	31	280
Illnesses during pregnancy*				
Fever				
Yes	9	8	6	57
Vag/cx infection				
Yes	16	16	13	124
UTI				
Yes	14	24	16	155
Medications during pregnancy*				
Any				
Yes	95	86	87	829
Aspirin				
Yes	11	8	5	51
NSAID				
Yes	4	16	8	73
Acetaminophen				
Yes	46	38	49	455
Antibiotic				
Yes	32	32	31	296
Maximum column N	61	41	885	987

Abbreviations:
BMI = Body mass index
IVH = Intraventricular hemorrhage
NSAID = Nonsteroidal anti-inflammatory drug
UTI = Urinary tract infection
Vag/Cx = Vaginal/cervical infection
* Can be in more than one category.

clinical information. Each set of scans was first read by a study sonologist at the institution of the infant's birth. The images, usually electronic images imbedded in the software eFilm Workstation (Merge Healthcare/Merge eMed, Milwaukee, WI) and written to a CD, were sent to a sonologist at another ELGAN study institution for a consensus reading. The eFilm program allowed the second reader to see what the first reader saw and provided options to replicate the viewing conditions of the original reader, including the ability to zoom and alter image contrast and brightness. When the two readers differed in their recognition of IVH, moderate to severe lateral ventricle enlargement, one or more hyperechoic (echodense) lesion(s) in the parenchyma, or one or more hypoechoic (echolucent) lesion(s) in the parenchyma, the films were sent to a third (tie-breaking) reader who did not know what the other sonologists reported.

IVH was diagnosed when hyperechoic material was seen in the lateral ventricles or was adherent to the choroid plexus. The ultrasound data collection form also included a provision for the sonographer to assign a diagnosis to white matter lesions that are sometimes made in ELGANs, either PVL or PVHI. However, diagnostic criteria for these entities were not included in the procedures manual. Further, no efforts were made to minimize observer variability with regard to PVL or PVHI, as consensus for these diagnostic labels was not sought.

The data collection forms required that information about hyperechoic and hypoechoic lesions be recorded for every one of 16 white matter zones in each cerebral hemisphere on coronal imaging (see figure 1 in Westra et al. [7]). Agreement among readers was not required for the number of lesions. Rather, we accepted the number of boxes checked off by the first of the two readers who agreed on the presence of a hyperechoic or hypoechoic lesion.

Newborn variables

The gestation estimates were based on a hierarchy of the quality of available information. Most desirable were estimates based on the dates of embryo retrieval or intrauterine insemination or fetal ultrasound before week 14 (62%). When these were not available, reliance was placed sequentially on a fetal ultrasound at 14 or more weeks (29%), last menstrual period without fetal ultrasound (7%), and gestation recorded in the log of the neonatal intensive care unit (1%).

The birth weight *z* score is the number of standard deviations the infant's birth weight is above or below the median weight of infants at the same gestation in a standard dataset [10].

We collected all physiologic, laboratory, and therapy data for the first 12 postnatal hours, which were needed to calculate a Score for Neonatal Acute Physiology-II (SNAP-II) [11]. Twenty-eight percent of the sample had a SNAP-II value >30 and 32% had a SNAP-Perinatal Extension-II (SNAPPE-II) value >45. We also identified cutoffs for each week of gestation that defined the top quartile and top decile of SNAP-II and SNAPPE-II.

On days 7, 14, 21, and 28, information was collected summarizing findings of the preceding week, including results of bacterial cultures of blood, and trachea and cerebrospinal fluids; receipt of blood products and methylxanthines; and new diagnoses, such as PDA, necrotizing enterocolitis, and retinopathy of prematurity.

Mode of ventilation for the first 7 postnatal days was defined as the highest level of support on each day ranging from no support, increased ambient oxygen in a hood, nasal cannula, nasal continuous positive airway pressure, and conventional mechanical ventilation to high-frequency ventilation. After the first week, this information was collected on days 14, 21, and 28, and at 36 weeks postmenstruation. The specific devices used for respiratory support were not recorded. The number of days each infant received supplemental oxygen, continuous positive airway pressure, and mechanical ventilation (including high-frequency ventilation) was recorded.

The timing of blood gas analyses was not based on a protocol, but on the needs of each infant, as judged by the clinician. The number of blood gases obtained on each day declined rapidly during the first postnatal week and varied among the participating institutions.

ELGANs were classified by their extreme blood gas measurements on postnatal days 1, 2, and 3. For each of these days, the lowest, highest, and mode (most common) value for partial pressure of arterial oxygen (P_aO_2), partial pressure of arterial carbon dioxide (P_aCO_2), and arterial pH were recorded. The modal PaO_2 on postnatal days 7 and 14 was classified, and it was noted if the infant did not have a blood gas assessment on those days. In the sample, blood gas measurements that defined the extreme

Table 3. Characteristics of the delivery of children with hypoechoic lesions with or without IVH (column percents)

Characteristics of Delivery	Hypoechoic Lesion			Total
	Yes		No	
	IVH		IVH	
	Yes	No	No	
Antenatal steroid course				
Partial	21	20	27	260
None	20	10	9	98
Magnesium				
For tocolysis	58	59	59	530
Seizure prophylaxis	7	5	15	136
Delivery mode				
Cesarean	52	46	70	668
Pregnancy complication				
Preterm labor	61	54	43	437
Preterm PROM	16	20	22	210
Preeclampsia	7	5	16	145
Abruption	3	2	11	97
Cervical insufficiency	8	7	5	50
Fetal indication	5	12	5	48
Duration of labor				
>0 to ≤12 hours	33	29	20	212
>12 hours	52	59	51	508
Duration of membrane rupture				
1-24 hours	23	22	15	159
>24 hours	16	17	26	244
Number of fetuses				
≥2	38	24	32	320
Sex				
Male	69	41	52	506
Gestational age (weeks)				
23-24	46	20	19	207
24-25	41	46	45	440
Birth weight (grams)				
≤750	52	29	39	390
751-1000	31	49	42	410
Birth weight *z* score*				
<−2	3	2	7	66
≥−2, <−1	13	7	15	142
Maximum column N	61	41	885	987

Abbreviations:
IVH = Intraventricular hemorrhage
PROM = Premature rupture of membranes
* External standard is the Oxford UK dataset [10].

Table 4. Characteristics of the placentas of children with hypoechoic lesions with or without IVH (column percents)

Placenta Characteristics	Hypoechoic Lesion			Total
	Yes		No	
	IVH		IVH	
	Yes	No	No	
Placenta micro-organisms				
Number of species isolated				
1	34	21	23	213
≥2	39	33	24	222
Any organism	73	54	47	435
Aerobe	59	28	31	286
Anaerobe	38	36	28	256
Mycoplasma	11	13	10	91
Skin organisms[skin]	41	26	20	194
Vaginal organisms[vag]	23	13	16	145
Maximum column N	56	39	793	888
Placenta histology				
Inflammation of the chorionic plate*	32	22	19	181
Inflammation of the chorion/decidua†	49	36	36	335
Neutrophils in fetal stem vessels	36	31	25	229
Umbilical cord vasculitis‡	17	11	17	147
Thrombosis in fetal stem vessels	9	3	6	55
Infarct	9	30	19	169
Increased syncytial knots	15	11	22	193
Decidual hemorrhage/fibrin deposition	19	36	16	155
Maximum column N	53	37	831	921

Abbreviations:
IVH = Intraventricular hemorrhage
[skin] = *Corynebacterium* sp, *Propionibacterium* sp, *Staphylococcus* sp
[vag] = *Prevotella bivia*, *Lactobacillus* sp, *Peptostrep magnus*, *Gardnerella vaginalis*
* Stage 3 and severity 3.
† Grades 3 and 4.
‡ Grades 3, 4, and 5.

quartiles varied by gestation and postnatal day. Consequently, infants were classified by whether or not their extreme value (for each day) was in the extreme quartile for their gestation (23-24, 25-26, and 27 weeks). Because an extreme measure on one day could reflect a fleeting event, we required that an infant be in the extreme quartile on at least two of the 3 days to be considered "exposed" to such extremes. Because we did not record if the extreme pH and P_aCO_2 measurements were temporally paired, we did not calculate base deficits.

We did not specify a priori the method (oscillometry or intra-arterial catheter) for measuring arterial pressure (MAP) or the frequency with which MAP measurements were to be recorded, and research personnel who abstracted data were unaware of the method. We recorded the lowest, highest, and mode (most common) MAP in the first 24 postnatal hours, when blood pressures tend to be their lowest [12-14]. Three dichotomous hypotension indicators were evaluated. The first, "MAP in the lowest quartile for gestational age," is based on the distribution of the lowest recorded MAPs in the sample. The second, "vasopressor treatment," is an operational definition based on the assumption that hypotension is likely to be clinically significant if the neonatologist perceived the need to treat with a vasopressor. The third indicator, "blood pressure lability," identified infants whose difference between the highest and lowest MAP during the first 24 hours was in the highest quartile for gestation in this sample.

Documented early bacteremia was defined as recovery of an organism from blood drawn during the first postnatal week, and late bacteremia as recovery of an organism from blood drawn during weeks 2, 3, or 4. Specific organisms were not identified. A diagnosis of tracheal colonization required the recovery of a pathogen from tracheal aspirate.

The diagnosis of PDA was assigned by the clinician based on his or her clinical judgment without uniformity of definition. The presence of PDA was recorded as either "clinically suspected" or "echocardiographically confirmed." PDA therapy included either pharmacologic closure (indomethacin or ibuprofen lysine) or surgical ligation.

Data analysis

We evaluated the null hypothesis that the risk profile of an isolated hypoechoic lesion does not differ from that of a hypoechoic lesion accompanied or preceded by IVH. Tables 2 through 5 display univariable analyses of relationships between potential antecedents or confounders (left column) and the outcomes of interest (isolated hypoechoic lesions and hypoechoic lesions accompanied by IVH), including the reference group, consisting of infants who had neither a hypoechoic lesion nor IVH. From Tables 2 through 4, we selected antenatal variables as potential antecedents or confounders if they were associated with either outcome with a *P* value of ≤0.25 [15]. From Table 5 we selected postnatal variables. No *P* values are presented in this table because we did not seek statistical significance of isolated differences. Statistical significance is the focus of Table 6, which evaluates multiple variables in light of one another.

Table 5. Characteristics and exposures of children with hypoechoic lesions with or without IVH (column percents)

Characteristics & Exposures	Hypoechoic Lesion			Total
	Yes		No	
	IVH		IVH	
	Yes	No	No	
SNAP-II				
≥30	48	13	20	205
P_aO_2 in lowest quartile*				
Yes	33	21	19	165
P_aO_2 in highest quartile*				
Yes	17	10	19	153
P_aCO_2 in lowest quartile*				
Yes	17	24	19	157
P_aCO_2 in highest quartile*				
Yes	33	10	19	161
pH in lowest quartile*				
Yes	38	10	17	152
P_aO_2 week 1				
<42†	7	10	7	73
P_aO_2 week 2				
<41†	13	10	4	49
Lowest quartile MAP				
Yes	21	17	19	182
Vasopressor‡				
Yes	34	22	20	209
Labile MAP§				
Yes	23	22	24	228
Surfactant (first week)				
Yes	98	80	90	886
Methylxanthine^{MX} (days)				
≥15	31	61	63	598
Postnatal steroid^{PS}				
Yes	23	17	13	133
Analgesics				
Yes	95	73	65	664
Sedative				
Yes	33	34	24	242
PDA treatment				
Yes	69	63	59	594
PDA surgical ligation				
Yes	23	12	13	135
PDA ligation after day 7				
Yes	20	12	11	116
Transfusion‖				
≥3 weeks	78	73	55	551
Tracheal infection				
Culture proven	31	21	21	214
Bacteremia (week 1)				
Culture proven	10	2	5	49
Bacteremia (weeks 2-4)				
Culture proven	39	37	24	252
Mech/hi-freq ventilation				
Day 7	89	66	54	582
Necrotizing enterocolitis (Bell stage)				
IIIa	2	2	1	11
IIIb	11	5	4	48
Isolated perforation	7	5	3	32
Retinopathy				
Stage ≥3	32	27	29	272
Zone 1	13	8	6	64
Maximum column N	61	41	885	987

Abbreviations:
IVH = Intraventricular hemorrhage
MAP = Mean arterial pressure
^{MX} = Aminophylline, theophylline, caffeine
PDA = Patent ductus arteriosus
^{PS} = Hydrocortisone or dexamethasone in weeks 1 or 2
SNAP-II = Score for Neonatal Acute Physiology-II

* In the lowest or highest quartile for gestational age on two of the first 3 postnatal days.
† Defines the lowest quartile.
‡ Vasopressor: drug treatment for hypotension in the first 24 hours (dopamine, dobutamine, epinephrine).
§ Labile MAP: labile blood pressure, defined as upper quartile of the difference in the lowest and highest MAP.
‖ Packed cells or whole blood during 3 of the first 4 postnatal weeks.

Because postnatal phenomena, such as the need for blood pressure support, can be influenced by antenatal phenomena, we created multivariable logistic regression models in which risk factors are ordered in a temporal pattern, so that the earliest occurring predictors or covariates of an outcome are entered first and are *not* displaced by later occurring covariates [16-21]. For the time-oriented risk models presented here, we have only two epochs: antenatal and postnatal. The antenatal component of multivariable analyses was created to serve as the main adjustment for postnatal exposures or characteristics. Variables from Table 5 were evaluated as potential candidates for the postnatal component of data presented in Table 6.

Because the outcomes are mutually exclusive and each is appropriately compared with the same referent group (i.e., children who had neither IVH nor a hypoechoic lesion), we used multinomial logistic regression for the evaluations of each antecedent. Each postnatal risk factor was evaluated individually by adding it to the multinomial model consisting of the antenatal set of potential confounders. Interaction terms were not evaluated.

The risks of a hypoechoic lesion, with and without IVH, associated with selected characteristics are presented as odds ratios (OR) and 99% confidence intervals. We selected this confidence interval rather than the conventional 95% confidence interval as a correction for multiple comparisons, while not appreciably increasing the risk of a type 2 (false-negative) error [22].

Results

Sample description

A total of 1190 ELGANs had a protocol 2 (days 5-14) or a protocol 3 (day 15 to postmenstrual week 40) scan on which two sonologists agreed on the presence or absence of a hypoechoic lesion in the cerebral white matter. Of these newborns, 885 had neither a hypoechoic lesion nor IVH.

As shown in Table 1, of the 61 children who had both hypoechoic lesions and IVH, 72% developed ventriculomegaly, 77% were given a diagnosis of PVHI, 39% were given a diagnosis of PVL, and more than half had unilateral hyperechoic lesions. Two-thirds of these children had a hypoechoic lesion in only one cerebral hemisphere. In contrast, of the 41 children who had an isolated hypoechoic lesion, only 15% developed ventriculomegaly, 5% were given a diagnosis of PVHI, 61% were given a diagnosis of PVL, and 41% had a hypoechoic lesion limited to one cerebral hemisphere.

Maternal and pregnancy characteristics

As shown in Table 2, indicators of low social class (e.g., low maternal educational attainment, public insurance) were overrepresented among children who developed an isolated hypoechoic lesion. Urinary tract infection in the mother during this pregnancy and maternal use of a nonsteroidal anti-inflammatory agent during this pregnancy were also more common among the children who developed an isolated hypoechoic lesion than among their peers who did not.

Delivery exposures and characteristics

As shown in Table 3, a fetal indication for preterm delivery was more common among newborns who developed an isolated hypoechoic lesion than among other newborns. Those who developed a hypoechoic lesion preceded or accompanied by IVH were more likely than newborns in the referent group to have been delivered because of preterm labor, to be boys, to have been born before week 25 of gestation, and to have a birth weight ≤750 g.

Table 6. Odds ratios and 99% confidence intervals

Characteristics & Exposures	Hypoechoic Lesion*	
	With IVH	Alone
Antenatal		
Gestational age (weeks)		
23-24	**8.1 (2.0, 33)**	1.0 (0.3, 4.2)
25-26	3.4 (0.9, 12)	1.1 (0.4, 3.4)
Birth weight > 1000 g	1.8 (0.5, 6.5)	1.5 (0.4, 5.0)
Male gender	2.1 (0.9, 4.5)	0.7 (0.3, 1.7)
NSAID during pregnancy	0.4 (0.1, 2.6)	2.2 (0.7, 7.6)
No corticosteroid	2.0 (0.8, 8.2)	0.7 (0.1, 3.6)
Preterm labor	1.8 (0.8, 4.0)	1.8 (0.7, 4.6)
Fetal indication	2.7 (0.5, 15)	**4.4 (1.03, 19)**
Bacteria in placenta		
Yes	2.2 (0.9, 5.3)	1.4 (0.6, 3.6)
Unknown	1.7 (0.4, 7.0)	0.6 (0.1, 4.6)
Postnatal		
SNAP-II ≥30	**2.3 (1.01, 5.2)**	0.3 (0.1, 1.7)
pH in lowest quartile on ≥2 days	**3.2 (1.4, 7.2)**	0.6 (0.1, 3.1)
Vasopressor	1.8 (0.8, 4.1)	1.4 (0.5, 3.9)
Analgesic	**7.7 (1.6, 37)**	2.2 (0.8, 6.7)
Transfusion in ≥3 weeks	2.2 (0.8, 6.4)	3.1 (1.00, 9.7)
Definite late bacteremia	1.8 (0.8, 3.9)	1.7 (0.7, 4.3)
Mech/hi-freq vent, day 7	**4.5 (1.3, 15)**	2.0 (0.7, 5.6)
Any PDA therapy (indomethacin &/or surgery)	1.3 (0.5, 2.9)	1.3 (0.5, 3.5)
Any PDA surgery	1.2 (0.6, 2.6)	1.3 (0.5, 3.2)
PDA surgery after day 7	1.5 (0.5, 4.9)	1.3 (0.3, 5.7)

Abbreviations:
IVH = Intraventricular hemorrhage
PDA = Patent ductus arteriosus
SNAP-II = Score for Neonatal Acute Physiology-II
Note: Odds ratios (99% confidence intervals) of the ultrasound entity that heads each column associated with the variables listed on the left. The referent group (not shown) consists of infants who had neither a hypoechoic lesion nor IVH. The antenatal component of these multinomial analyses is limited to antenatal variables. The postnatal component includes both antenatal and postnatal variables.
* Bold typeface signifies a statistically significant difference ($P < 0.01$) vs the referent group.

Placenta characteristics

As shown in Table 4, the placentas of newborns who developed hypoechoic lesions accompanied or preceded by IVH were more likely than those of other newborns to harbor any organism, an aerobe, or a skin organism. The placentas of these children were also more likely to have histologic inflammation of the chorionic plate, the chorion, or the decidua. In contrast, the placentas of newborns who developed isolated hypoechoic lesions were more likely to have an infarct or decidual hemorrhage with fibrin deposition.

First postnatal month characteristics

As shown in Table 5, an assortment of indicators of illness severity provided information about the odds of the entity characterized by both hypoechoic lesions and IVH. However, none of the potentially important antecedents or confounders we evaluated in Tables 2 through 4 was associated with increased odds of developing an isolated hypoechoic lesion.

Infants who developed a hypoechoic lesion with IVH were more likely than others to have a high SNAP-II during the first 12 hours, to have received a vasopressor (dopamine, dobutamine, or epinephrine) in the first 24 hours or analgesics during the first postnatal month, and were more likely to develop culture-documented bacteremia during the second through fourth weeks or surgically treated necrotizing enterocolitis (Bell stage IIIb). A P_aO_2 and pH in the lowest quartile, as well as a P_aCO_2 in the highest quartile on two of the first 3 postnatal days were each associated with hypoechoic lesions accompanied or preceded by IVH, as was being on a conventional or high-frequency ventilator on postnatal day 7.

Multivariable models

As shown in Table 6, in the antenatal multivariable model, only the youngest gestational age (23-24 weeks; OR = 8.1 [2.0, 33]) contributed statistically significant ($P < 0.01$) information about the risk of the combination of a hypoechoic lesion and IVH. When added individually to the antenatal model, a SNAP-II ≥30 (OR = 2.3 [1.01, 5.2]), a pH in the lowest quartile on two of the first 3 postnatal days (OR = 3.2 [1.4, 7.2]), receipt of an analgesic (OR = 7.7 [1.6, 37]), and being on a ventilator on postnatal day 7 (OR = 4.5 [1.3, 15]) were each associated with an increased risk of a hypoechoic lesion, if accompanied or preceded by IVH.

Only one antenatal variable, delivery for fetal indication (OR = 4.4 [1.03, 19]), was significantly associated with an isolated hypoechoic lesion. Receipt of a vasopressor added no information about the risk of isolated hypoechoic lesions (OR = 1.4 [0.5, 3.9]) nor did PDA therapy of any form (OR = 1.3 [0.5, 3.5]), surgical ligation at any time (OR = 1.1 [0.3, 3.2]), or surgical ligation after postnatal day 7 (OR = 1.3 [0.3, 5.7]).

Discussion

The major finding in this study is that the risk profile of an isolated hypoechoic lesion differs from that of a hypoechoic lesion accompanied or preceded by IVH. For example, those born at the lowest gestation were not at increased risk of isolated hypoechoic lesions but were at increased risk of hypoechoic lesions with IVH. In addition, a high SNAP-II, early recurrent or prolonged acidemia, receipt of an analgesic, and need for mechanical ventilation 1 week after birth were all risk factors for hypoechoic lesions with IVH but not for isolated hypoechoic lesions.

Isolated hypoechoic lesions and hypoechoic lesions with IVH as distinct entities

Experienced sonologists differ in their use of diagnostic labels (PVL or PVHI) when describing white matter lesions [7]. Some sonographers require the presence of bilateral lesions, usually posterior, for the diagnosis of PVL [23]. Others accept unilateral lesions as well [24]. In the ELGAN sample, more than one-third of the scans labeled “cystic PVL” had unilateral hypoechoic lesions [7]. To avoid these conflicts, we used descriptive terms (isolated hypoechoic lesions, or hypoechoic lesions accompanied by IVH) rather than diagnostic labels (PVL or PVHI). A single unilateral lesion was sufficient to classify a child as having an isolated hypoechoic lesion.

In the ELGAN study, PVL was less reliably identified than specific sonographic characteristics (e.g., hypoechoic lesions); nonetheless, the two entities were highly correlated in our sample. Only 5% of infants with isolated hypoechoic lesions were given the diagnosis of PVHI, while fully 77% of infants with hypoechoic lesions accompanied by IVH were given the diagnosis of PVHI (Table 1). Similarly, hypoechoic lesions accompanied by IVH were highly correlated with PVHI in our sample. Although 39% of infants with a hypoechoic lesion accompanied by IVH were diagnosed with PVL, a larger proportion of infants with isolated hypoechoic lesions were given the diagnosis of PVL (61%). These differences suggest that an ultrasound scan with an isolated hypoechoic lesion seems to be the signature of what many radiologists consider to be PVL, and an ultrasound scan of a hypoechoic lesion accompanied by IVH seems to be the signature of what many radiologists consider to be PVHI.

The findings in this study support the view that most isolated hypoechoic lesions can be viewed as a surrogate for the diagnosis of PVL, whereas hypoechoic lesions accompanied by IVH can be viewed as largely equivalent to PVHI. We urge caution in drawing inferences about PVHI and PVL, however, as use of the terms PVL and PVHI was not agreed upon by participating sonologists prior to the start of the study. In contrast, the data for both IVH and hypoechoic lesions are highly reliable because these characteristics (hypoechoic lesions, IVH) were carefully defined and agreed upon before any data were collected and had relatively low observer variability, and these lesions were read until consensus was achieved.

Relationship between hypotension and isolated hypoechoic lesions

Our attempt to extract normative data for blood pressure in ELGANs was hindered by the observation that clinicians differ considerably in the threshold that prompts intervention [12]. In the absence of a widely accepted definition of hypotension in ELGANs [12,25,26], we chose three definitions (see the section “Newborn variables”). To avoid the problems that accompany trying to identify the indication for treatment, we emphasized the treatment of hypotension, as the perceived need for treatment is likely the best proxy for clinically important hypotension.

In this sample, when potential antenatal confounders were considered, none of the indicators of systemic hypotension, including treatment with vasopressors, was associated with isolated hypoechoic lesions on serial cranial ultrasound. In the absence of an association between these hypotension indicators and hypoechoic lesions, no support was found for a relationship between systemic hypotension, or its treatment, and isolated hypoechoic lesions, which were highly correlated with PVL in this sample.

The findings of this study are in agreement with the majority of published studies of the relationship between hypotension and perinatal cerebral white matter damage, which found no convincing evidence that hypotension increases the risk of hypoechoic lesions identified by cranial ultrasound [14,23,25,27-37]. The few studies that demonstrated an association between hypotension and white matter injury either failed to adjust for potential confounders (including treatment) or demonstrated a stronger relationship with hemorrhagic lesions (IVH, PVHI) than with hypoechoic lesions [38-42]. The one study that included an adjustment for treatment found that treated hypotension was significantly associated with PVL, while untreated hypotension was not [43]. The findings in this study are consistent with observations that treatment of hypotension does not reduce the risk of brain damage in preterm newborns [13,14].

Relationship between PDA, its treatment, and isolated hypoechoic lesions

Therapy to close a PDA is based on the assumption that closing the connection between the pulmonary artery and the aorta reduces the risk of bronchopulmonary dysplasia or chronic lung disease [44]. However, evidence is lacking that closing this connection either by surgical ligation or indomethacin reduces the risk of chronic lung disease or other morbidities [45,46].

A clinically significant PDA is usually accompanied by left-to-right shunting from the systemic to the pulmonary circulation and by a variable decrease in antegrade blood flow in the ascending and descending aorta (diastolic steal). Diastolic steal is frequently associated with systemic hypotension and has been posited as a mechanism for impaired cerebral perfusion of sufficient degree to cause PVL in preterm newborns [1,47]. After adjusting for potential confounders, however, no association was found between any treatment for PDA (early or late) and isolated hypoechoic lesions (Table 6).

Antecedents of hypoechoic lesions, accompanied or preceded by IVH

Although this study failed to identify antecedents of isolated hypoechoic lesions, it did find that several postnatal variables were associated with an increased risk of hypoechoic lesions, if preceded or accompanied by IVH. After adjusting for potential confounders, four postnatal variables (high SNAP-II, lowest quartile pH on at least two of the first 3 postnatal days, mechanical ventilation on day 7, and receipt of an analgesic) were associated with an increased risk of hypoechoic lesions with IVH (Table 6). Analgesic receipt can be viewed as a proxy for illness severity, as infants who require higher levels of cardiopulmonary support (ventilator, oxygen, and vasopressors) are more likely than their peers to receive analgesics [12]. The findings suggest that low gestation and correlates of postnatal illness severity appear to increase the risk of hypoechoic lesions, only if accompanied or preceded by IVH, which in this study correlated strongly with PVHI (Table 6).

In the ELGAN study, hyperoxemia, hypocapnia, hypercapnia, and acidemia all predicted ventriculomegaly [48], while none of these derangements predicted hypoechoic lesions (with or without IVH). Our analyses from the same dataset, however, demonstrate that hypoechoic lesions accompanied by IVH were significantly associated with blood gas derangements, while isolated hypoechoic lesions were not. This and other differences support our hypothesis that white matter injury, if accompanied or preceded by IVH, appears to have a different causal pathway than white matter injury that occurs in the absence of IVH.

Limitations

Although both intravascular catheters and oscillometry were used to collect blood pressure data, we cannot be certain that the lowest blood pressure for the day was recorded. Our findings might have been confounded by the use of volume expansion, as approximately 75% of our sample received volume expansion in the first 24 hours [12]. The study also lacks quantitative information about the severity of ductal shunting with a PDA. The most important limitation of this and other studies of the link between low blood pressure and brain damage is that they are frequently confounded by the physician's perception that intervention is needed. Eliminating the bias that follows (i.e., "confounding by indication") seems to be an almost impossible task [49].

Strengths

This study enrolled newborns based on gestation criteria, whereas the only published study to date that evaluated infants with isolated PVL [1] enrolled patients on the basis of birth weight [50]. In that study, the authors excluded newborns with grade 3 IVH, PVHI, congenital anomalies of the central nervous system, hypoxic-ischemic encephalopathy, and death before hospital discharge [1]. By including infants with IVH and PVHI in the current study, we were better able to identify potential antecedents and confounders of the relationship between hypoechoic lesions with and without IVH. Moreover, this study reflects associations related to the clinical practice of 14 different university-affiliated hospitals and medical centers.

Implications for clinicians and researchers

In a sizable proportion of ELGANs without a hypoechoic lesion, white matter damage can first be identified on a brain magnetic resonance imaging at term gestation [51]. Moreover, almost one-third of ELGANs with normal cranial ultrasounds will have functional developmental impairments at follow-up [21]. Nonetheless, echolucency with and without IVH are important short-term indicators of white matter damage associated with long-term impairments [2,52,53].

The differences in risk profiles between isolated hypoechoic lesions and hypoechoic lesions accompanied or preceded by IVH have the potential to provide insights into the pathogenesis of white matter injury. Since low gestational age and illness severity are the most obvious antecedents of echolucency accompanied or preceded by IVH, neonatologists and neonatal neurologists are probably less able than perinatologists to reduce the occurrence of this entity.

Conclusions

In this large, multicenter sample of ELGANs, the risk profile of a hypoechoic lesion unaccompanied by IVH differs from that of a hypoechoic lesion with IVH. This suggests that hypoechoic lesions accompanied or preceded by IVH (our surrogate for PVHI) may have a different causal pathway than isolated hypoechoic lesions (our surrogate for PVL). Thus, these two entities can be regarded as two subtypes of white matter damage, based on differences in epidemiologic features.

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