Lenticulostriate vasculopathy in preterm infants: a new classification, clinical associations and neurodevelopmental outcome

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Abstract

Objective To examine the inter-rater reliability for the diagnosis of LSV on cranial ultrasound (cUS), determine the risk factors associated with LSV and its progression, and examine neurodevelopmental outcome.

Study design Prospective case–control study of neonates ≤32wks of gestation assessed for LSV by serial cUS ($n = 1351$) between 2012 and 2014 and their neurodevelopment at 18–36mon-corrected age compared to controls.

Results Agreement for LSV on cUS improved from Kappa 0.4–0.7 after establishing definitive criteria and guidelines. BPD was the only variable associated with the occurrence and the progression of LSV. Cytomegalovirus (CMV) infection occurred in one neonate (1.5%). Neurodevelopmental outcome of neonates with LSV did not differ from controls.

Conclusions Establishment of well-defined stages of LSV improves the reliability of the diagnosis and allows identification of neonates with progression of LSV. Although LSV was associated with BPD, it was not associated with congenital CMV infection.

Introduction

Lenticulostriate vasculopathy (LSV) was first reported 30 yrs ago on a cranial ultrasound (cUS) obtained on a preterm neonate with congenital cytomegalovirus (CMV) infection. These hyperechogenic lines within the deep gray matter were located in the area of lenticulostriate vessels and differed from the clumped shadowing echogenicities associated with calcifications [1]. Teele et al. subsequently

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published the first retrospective case series of 12 neonates with LSV [2]. Eight of the neonates had evidence of congenital TORCH infections (toxoplasma, others, rubella, cytomegalovirus, and herpes). In the following years, LSV became synonymous with the presence of congenital infection. However, in more recent studies numerous non-infectious etiologies have been observed to be associated with the presence of LSV on cUS, including hypoxic-ischemic events, chromosomal anomalies, inborn errors of metabolism, fetal alcohol exposure, and congenital anomalies [3]. Thus, the pathogenesis of LSV remains unclear.

The presence of LSV is best determined by cUS. Neither computerized axial tomography nor magnetic resonance imaging have consistently demonstrated corresponding abnormalities when hyperechogenic lines were detected in the supratentorial deep gray matter structures by cUS [4–7]. Doppler blood flow studies subsequently demonstrated arterial signals within the hyperechogenic lines in the basal ganglia and thalamus, supporting the view that LSV represents a vascular lesion [4, 8–12]. Although LSV is best detected by cUS, the radiographic definition is vague and inter-rater reliability has generally been poor [13]. Thus, the presence of "hyperechogenic lines in the basal ganglia and/

or thalamus" may be insufficient following the technological advances in cUS imaging, which demonstrate an enhanced pattern of echos and may result in false positive conclusions. These advances may also enhance detection of LSV and allow for studies of the progression of LSV after birth; but this would require a better definition of the changes in echogenicity that occur.

The primary aim of this prospective case–control study was to evaluate the inter-rater reliability of cUS recognition of LSV among pediatric radiologists and determine if this could be improved after implementing a predefined standardized classification of LSV. In addition, we sought to assess the incidence of LSV, determine the association with congenital CMV infection, examine if LSV is associated with specific clinical risk factors, and determine if LSV is associated with altered neurodevelopment in preterm neonates ≤32wks gestational age (GA).

Methods

This is a prospective case–control study of neonates ≤32wks GA admitted to the Neonatal Intensive Care Unit (NICU) at Parkland Hospital, Dallas, TX between January 2012 and June 2014. The study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center and Parkland Health and Hospital Systems. Parental consent was obtained prior to enrollment. All neonates ≤32wks GA admitted to the NICU have cUS scans at 3–5 days (and/or 7–10 days) and 30-day postnatal and at discharge [14]. They are performed by skilled ultrasound technicians using the Siemens Acuson Sequoia 512 Ultrasound systems with high frequency 8 Hz transducer. Standard coronal and sagittal images were obtained from the anterior fontanel. Mastoid views were obtained through the posterior fontanel. All of the cUS were prospectively reviewed for the presence of LSV by a team of pediatric radiologists assigned to the NICU. To assess the variance in readings, we established three readers. Reader A included "all" of the radiologists who routinely evaluated cUS on a daily basis ($n = 9$ physicians that include both study radiologists); Reader B was the study radiologist (MP), who prospectively evaluated all cUS for absence or presence of LSV; Reader C was another study radiologist (DW), who independently evaluated the cUS when there was a disagreement between the Readers A and B or if Readers A and B were the same reader in order to establish a consensus. Both study radiologists were blinded to the interpretations of the all other radiologists, including each other. The diagnosis of LSV was based on the recognition of a lesion defined as "hyperechogenic lines within the basal ganglia and/or thalamus on both coronal and parasagittal views on cranial ultrasound". All neonates identified to have

LSV by either Reader A or B were included in the study. Neonates were excluded if a consensus was not established by at least two radiologists (Readers A and B, Readers B and C, or Readers A and C). In order to establish a more standardized and consistent method for determining the presence of LSV and assessing its extent, we introduced a new grading system for LSV in February 2013 (Fig. 1): Stage 0 had no hyperechoic lines/vessels; Stage 1 included the presence of lenticulostriate vessels that were considered thin and faintly seen; Stage 2 included vessels that were considered thin, but hyperechogenic; and Stage 3 included vessels that were considered thick and hyperechogenic, i.e., the echogenicity resembled that seen in the Sylvian fissure. All the cUS of neonates with LSV obtained prior to February 2013 were blindly re-evaluated by Readers B and C and the new classification system used to assign staging and assess the progression of LSV. The highest stage LSV agreed on by at least two radiologists was then used to subsequently group the neonates for severity of LSV.

In order to determine what clinical data are associated with the presence and/or progression of LSV on cUS, we prospectively collected the following data: prenatal risk factors including maternal age, race, ethnicity and gravida, multiple births, maternal drugs used in pregnancy, maternal diabetes and hypertension. Additional risk factors included administration of antenatal steroids, maternal chorioamnionitis, prolonged rupture of membranes >18 h, any fetal distress, meconium stained amniotic fluid, mode of delivery and exposure to intrapartum magnesium sulfate. Postnatal risk factors included birth weight (BW), head circumference, GA, gender, Apgar scores and umbilical artery pH, base excess, and PaO_2, and admission temperature. Preterm infants who were small for gestational age (SGA) or had a birth weight <25th centile were identified as a potential proxy for chronic intrauterine hypoxia [15]. Neonatal morbidity was also assessed and included: respiratory distress syndrome (RDS), symptomatic patent ductus arteriosus, congenital and acquired pneumonia, transient tachypnea of newborn, pulmonary artery hypertension, pulmonary hemorrhage, apnea of prematurity, sepsis, necrotizing enterocolitis (NEC; only Stage 2 and 3), bronchopulmonary dysplasia (BPD), pulmonary interstitial emphysema, pneumothorax, surfactant administration, inhaled nitric oxide administration, number of ventilator days, sepsis, retinopathy of prematurity, ICH, PVL, VM, neonatal hypoxic encephalopathy, and hypothyroidism (defined as if treatment was required). The presence of congenital CMV infection was determined by maternal serology and urine CMV cultures obtained at the time of first cUS with LSV. Evaluation of congenital infections in the control neonates was limited to maternal serology or presence of clinical manifestations. None of the control patients showed clinical stigmata of CMV infection.

Fig. 1 Proposed classification for staging LSV on parasagittal cUS in the neonate. **a** Stage 0: Lenticulostriate vessels are not visible on gray scale image. **b** Stage 1: Faint linear echogenicities corresponding to a lenticulostriate artery (arrow). **c** Stage 2: Thin hyperechogenic lenticulostriate vessels (arrows). **d** Stage 3: Lenticulostriate vessels are thick (solid arrows) and echogenicity equals sulci (dashed arrow)
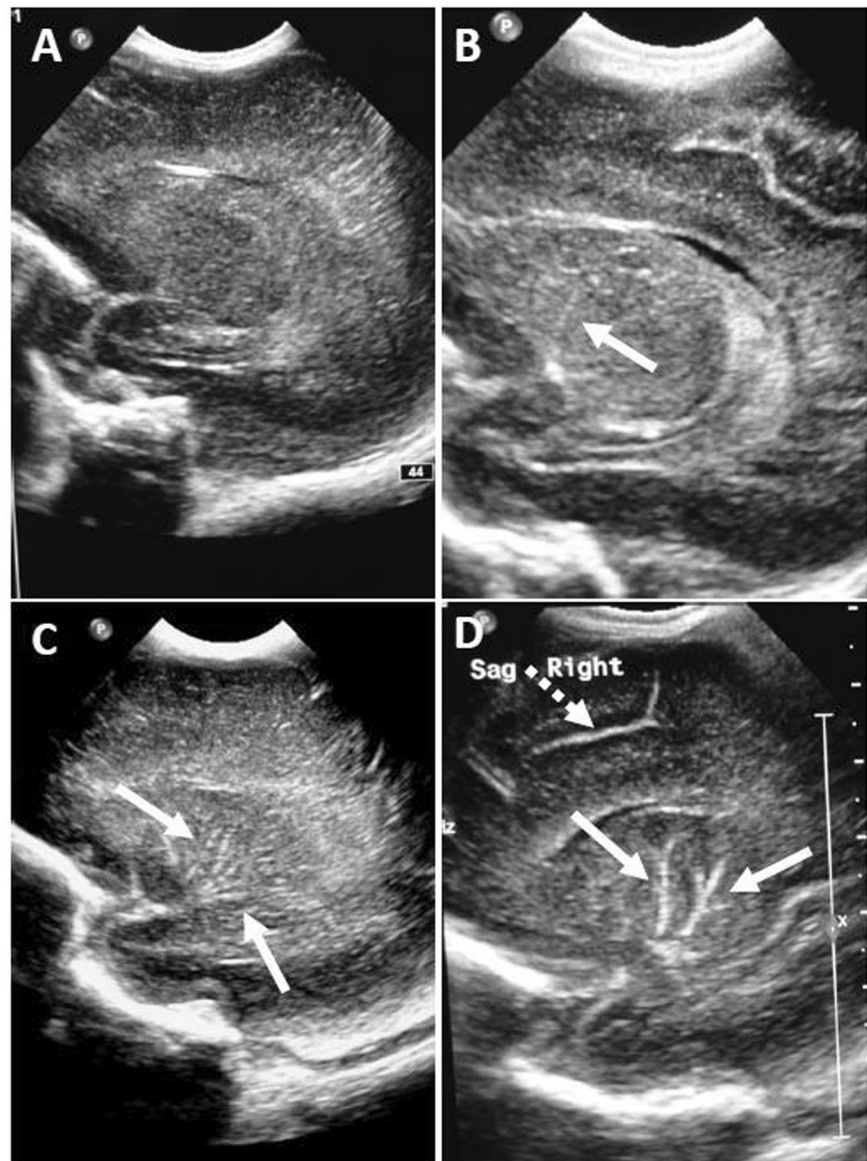
All neonates enrolled in the study were scheduled for follow-up and neurodevelopmental assessment at 18–36mon adjusted age in the Thrive Clinic at the Children's Medical Center at Dallas. Infants were classified as having neurodevelopmental impairment (NDI) based on the Bayley Scales of Infant and Toddler Development (BSID) version III, which is assessed at 18–36mon-adjusted age. The Bayley III threshold for moderate-to-severe NDI was defined as having a cognitive composite score >1 SD below the mean (<85) and/or a motor composite score <73. The latter threshold was based on data from the Neonatal Research Network, which demonstrated that <73 was more sensitive and specific for detecting moderate-to-severe gross and/or fine motor impairment than a cutoff of <85, though the latter had been shown to be better for cognitive [16]. In

order to have a comparison group, we also enrolled GA and gender matched controls. We matched each infant with LSV 1:1 with the next infant born following who had the same GA (completed weeks of gestation) and gender without evidence of LSV, intracranial hemorrhage (ICH), periventricular leukomalacia (PVL), or ventriculomegaly (VM) on any of the cUS scans by discharge.

Statistical analysis

Statistical analyses were performed using SPSS software version 19. We calculated the sample size based on incidence estimate and precision. A sample size of 360 would need to be evaluated assuming a LSV incidence of 5–20% or 18–72 infants with LSV with a narrow 95% confidence

Table 1 Kappa analysis comparing the readings of cranial ultrasound scans for the absence and presence of lenticulostriate vasculopathy by Readers A and B and then Reader B and C before and after implementation of the new classification

	Before		After	
	Reader B		*Reader B*	
Reader A	Absent	Present	Absent	Present
Absent	589	46	583	45
Present	2	22	0	64
Kappa	0.44 (95% CI: 0.32–0.57)		0.70 (95% CI: 0.62–0.78)	
	Reader C		*Reader C*	
Reader B	Absent	Present	Absent	Present
Absent	48	4	2	0
Present	13	55	0	62
Kappa	0.71 (95% CI: 0.59–0.84)		1.00 (95% CI: 1.00, 1.00)	

Reader A represents the group interpretations, whereas Readers B and C are independent readers

interval (half width of 2–4%). Kappa statistics were used to assess inter-rater reliability between the three readers described above. Kappa >0.20 is considered to be "fair" agreement, 0.40 "moderate" agreement, 0.60 "good" agreement and >0.80 "excellent" agreement [17]. Categorical variables were analyzed by χ^2 analysis and continuous variables for multiple groups by analysis of variance (ANOVA). If the ANOVA had a $P < 0.05$, differences between groups were determined using pairwise analysis and a Bonferroni correction method. Logistic regression analysis was conducted to examine the relationships between stages of LSV and NDI. Multinomial logistic regression analysis with forward selection of variables that could be associated with occurrence or progression of LSV (GA, BW <10th and <25th centile, cesarean delivery, male gender, multiple birth, maternal chorioamnionitis, antenatal steroids, Apgar scores, RDS, BPD, apnea, NEC and hypothyroidism) was performed in order to identify the variables that predict the occurrence and/or progression of LSV. Variables are summarized as percentages and means ± standard deviation (SD). All statistical tests used a significance level of 0.05.

Results

Validation of cUS readings

Total of 445 neonates ≤32wks GA were admitted to the NICU during the study period. Four hundred and seven had at least one cUS performed. Of the 407 neonates studied, there were 1351 cUS available for evaluation. LSV was identified in 70/407 neonates by either Reader A or B on at least one cUS; the agreement by both readers was 50/70 (71%). Reader C evaluated the remaining 20 neonates' cUS and LSV confirmed in 15; thus incidence of LSV on cUS in neonates ≤32wks GA was 15% (65/407).

Of the 1351 cUS available, 659 cUS were obtained prior to introducing the new classification. Seventy (11%) cUS were read as positive for LSV by Readers A and B. There was disagreement on 48 resulting in a Kappa of 0.44 (Table 1). In contrast, there was good inter-rater reliability between Readers B and C, who agreed on the presence of LSV on 55 cUS, absent on 48 and disagreed on 17, Kappa 0.71 (Table 1). After implementing the new classification for LSV on cUS in February 2013, there were 692 cUS available for review. Of these, 109 (16%) had a least one reading positive for LSV. Readers A and B agreed 64/109 were positive for LSV and disagreed on 45 cUS. Importantly, the Kappa improved to 0.70 (Table 1), while the agreement between Readers B and C improved to 100%.

Clinical variables associated with LSV

In order to assess the clinical variables associated with the occurrence of LSV on cUS, we divided the study neonates into four groups according to their highest stage of LSV: Stage 0 included the controls, none of whom had LSV, and LSV Stage 1, 2, or 3 included neonates as defined above. Groups did not differ from each other for any of the variables examined (Table 2). However, when a stepwise regression analysis was performed, BPD was associated with the occurrence of LSV [$P = 0.02$; odds ratio (OR) = 2.9; 95% CI = 1.1–7.2]. Four of the 135 infants studied (65 LSV and 70 control) died, all had LSV; 3 died from severe BPD and 1 with *E. coli* sepsis. Urine CMV cultures were performed in 98% (64/65) of neonates with LSV at the time of initial cUS diagnosis, mean postnatal age of 18 days (95% CI = 15–22 d). Only one (1.5%) of these neonates tested positive for congenital CMV infection and the neonate was at 7d postnatal age.

Onset and progression of LSV

We assessed the age at first diagnosis and if there was progression of LSV after birth. Neonates with Stage 1 LSV ($n = 22$) were more likely to be diagnosed after 15d postnatal, the incidence increasing from 13% at 1–4d to 74% after 15d (mean 27d; 95% CI = 19–35d). Stage 2 ($n = 31$) and Stage 3 ($n = 12$) LSV were more likely to be first observed on cUS at an earlier age (mean 14d; 95% CI = 11–18d), with 60% presenting <15d postnatal and 40% after 15d ($P = 0.04$, χ^2) (Fig. 1, Supplementary material).

We were able to evaluate the progression of LSV on 248 serial cUS (mean number of cUS for each neonate was

Table 2 Maternal and neonatal demographics and clinical characteristics associated with the different stages of lenticulostriate vasculopathy determined from the highest stage diagnosed

	Control (n = 70)	Stage 1 (n = 22)	Stage 2 (n = 31)	Stage 3 (n = 12)	P value[c]
Maternal age (yrs)	28 ± 7[a]	29 ± 7	31 ± 8	27 ± 8	0.2
Race/ethnicity					0.33
White Non-Hispanic	8 (11)[b]	1 (5)	2 (7)	1 (8)	
Black Non-Hispanic	8 (11)	6 (27)	4 (13)	5 (33)	
Hispanic	54 (77)	15 (68)	25 (80)	7 (58)	
Maternal diabetes	12 (17)	1 (5)	4 (13)	0 (0)	0.23
Maternal hypertension	29 (41)	8 (36)	13 (42)	1 (8)	0.17
Chorioamnionitis	5 (7)	1 (5)	3 (10)	1 (8)	0.92
Antenatal steroids	33 (47)	14 (64)	11 (36)	9 (75)	0.06
Magnesium exposure	33 (47)	9 (41)	15 (48)	2 (17)	0.24
Cesarean delivery	56 (80)	16 (73)	24 (77)	8 (67)	0.73
Gestational age (wk)	29 ± 2	29 ± 2	30 ± 2	29 ± 3	0.83
Birth weight (g)	1221 ± 263[a]	1187 ± 319[a]	1340 ± 378[a]	1459 ± 540[a]	0.05
Birth weight ≤10th centile	11 (15)	4 (18)	4 (13)	1 (8)	0.87
Birth weight <25% centile	26 (37)	7 (32)	9 (29)	2 (16)	0.53
Male	31 (44)	8 (35)	14 (47)	5 (42)	0.84
Umbilical artery pH	7.26 ± 0.08	7.25 ± 0.09	7.22 ± 0.10	7.27 ± 0.08	0.20
Umbilical artery base deficit	−6 ± 3.2	−6 ± 3.8	−7 ± 4.6	−5.6 ± 2.6	0.37
RDS	47 (67)	16 (73)	22 (71)	9 (75)	0.92
BPD	10 (14)	5 (23)	9 (29)	4 (33)	0.23
NEC	0 (0)	0 (0)	2 (7)	0 (0)	0.21
HIE	0 (0)	0 (0)	1 (3)	0 (0)	0.34
ROP	19 (27)	7 (32)	5 (16)	4 (33)	0.50
Hypothyroidism	2 (3)	2 (9)	2 (7)	2 (17)	0.25
Congenital CMV	NA	0 (0)	0 (0)	1 (1)	0.11
PVL	NA	3 (14)	3 (10)	0 (0)	0.42
ICH	NA	4 (18)	8 (26)	4 (33)	0.61
Mortality	NA	1(5)	1 (3)	2 (17)	0.24

RDS respiratory distress syndrome, *BPD* bronchopulmonary dysplasia, *NEC* necrotizing enterocolitis, *HIE* hypoxic-ischemic encephalopathy, *CMV* cytomegalovirus, *PVL* periventricular leukomalacia, *ICH* intracranial hemorrhage

[a]Values are presented as means ± SD

[b]Values in parentheses are the percent of the total population within a column

[c]Data analyzed by ANOVA for continuous variables and χ^2 for categorical variables. When ANOVA was $P < 0.05$, Bonferroni's pairwise analysis was performed to separate groups; significant differences between groups across rows are noted by different superscripts

3.8; 95% CI = 3.6–4.1). This included all neonates with LSV. Sixty-seven percent of neonates (44/65) with LSV showed progression from Stage 0: 19 neonates from Stage 0 to 1, 18 neonates from Stage 0 to 2 and 7 neonates from Stage 0 to 3. When we compared neonates who progressed from Stage 0 to 1, 2, or 3 to control neonates, those

progressing to Stage 2 were more likely to have BPD ($P = 0.02$), NEC ($P = 0.02$) and infants progressing to Stage 3 were more likely to have hypothyroidism ($P = 0.04$, ANOVA). (Table 1, Supplementary material). BPD was the only clinical variable associated with LSV progression from Stage 0 to 2 ($P = 0.003$; OR = 7; 95% CI = 1.9–25) by multinomial logistic regression analysis; progression to Stage 3 was not significant due to the small number of neonates ($n = 7$; $P = 0.1$, OR = 3.6; 95% CI = 0.6–20).

Neurodevelopmental outcome

Forty infants with LSV (66%) completed follow-up at 18–36mon-corrected age; 4 died before discharge, 8 were seen before 18mon, and 13 were lost to follow-up. Twenty-nine of the 40 infants had isolated LSV with no evidence of ICH, PVL, or VM on cUS while 11 had LSV Plus (LSV with ICH, PVL, or VM) (Table 3). When these two groups were compared to the 48 control infants who were seen at 18–36mon-corrected age (48/70, 69%), there were no significant differences for any measurement of neurodevelopment outcome between the three groups (Table 3). We also determined if the 40 infants with LSV who completed follow-up differed from the 21 infants who were either lost to follow-up or seen before 18mon. There were no significant differences in any of the demographics or clinical variables, except those who completed follow-up had lower birth weight ($P = 0.01$) and GA ($P < 0.01$). When the risk for NDI was classified by the stage of LSV and assessed by logistic regression analysis, there were no significant differences between Stage 1 (OR = 0.54, 95% CI = 0.17, 1.71) or Stages 2 + 3 (OR = 1.52, 95% CI = 0.61, 3.78) LSV and controls (Table 2, Supplementary material).

Discussion

Although LSV has been observed on cUS in preterm neonates by numerous investigators, important gaps of knowledge remain regarding validation of the cUS readings, progression on serial cUS and its effects on NDI at follow-up. Moreover, it remains unclear what factors are associated with the diagnosis of LSV on cUS. This is the first prospective study that not only provides a classification for neonatal LSV and its validation, but also examines the staging and progression of LSV as well as the neurodevelopmental outcomes in a contemporary cohort of preterm infants. The key observations are: (1) improved reliability of LSV diagnosis after establishing a well-defined classification of LSV on cUS, (2) strong association between BPD with LSV, (3) progression of LSV in preterm neonates with inflammatory diseases such as BPD and NEC, and (4)

Table 3 Comparison of neurodevelopmental outcomes in control preterm neonates, those with isolated lenticulostriate vasculopathy, and lenticulostriate vasculopathy plus other abnormalities on cranial ultrasound

	Control (n = 48)	Isolated LSV (n = 29)	LSV Plus (n = 11)	P value[a]
BSID mean chronologic age	2.3 ± 0.5	2.3 ± 0.4	2.3 ± 0.4	0.97
BSID mean corrected age	2.2 ± 0.5	2.1 ± 0.4	2.1 ± 0.4	0.68
Cognitive composite score	84 ± 9	83 ± 9	89 ± 8	0.21 (0.3[b])
Motor composite score	90 ± 8	89 ± 9	91 ± 9	0.76 (0.75[b])
Cognitive composite score <85	19 (39)[c]	14 (48)	3 (27)	0.46
Motor composite score <73	1 (2)	1 (3)	0 (0)	0.81
NDI (cognitive <85 or motor <73)	19 (39)	14 (48)	3 (30)	0.55

[a]One-way ANOVA

[b]Two-way ANOVA P value adjusted for BSID examination age

[c]Values in parenthesis are percent of total within a column

neurodevelopmental outcomes that do not differ from preterm controls.

Early reports suggested that the incidence of LSV in preterm neonates was on the order of 0.02–5% [8, 18–23]. More recently, it has been suggested that the incidence has increased and now ranges from 10–32% [7, 24, 25]. In our study, the incidence of LSV after validation of the cUS interpretation was 15% in neonates <32wks GA, suggesting the incidence may have increased in recent years. However, it is possible that improved ultrasound technology and increased awareness of this condition have contributed to the increased identification of neonates with LSV. Alternatively, the definitions of LSV on cUS might have been inadequate in the past.

Numerous investigators have consistently agreed that the lenticulostriate arteries are not normally visualized on cUS [2, 8, 21]. However, interpretation of echogenicity is often subjective; thus, consensus readings are essential to enhancing the diagnostic confidence [26, 27]. There are few reported studies that confirm the diagnosis of LSV by another reader and thus demonstrate validation [19, 28]. We previously reported in a retrospective study that Kappa values were quite low for the presence of LSV on cUS, 0.18 for cUS at 1–4d, 0.33 at 5–14d, and 0.36 at >15d postnatal, and showed no improvement with postnatal age [13]. El Ayoubi and Shin et al. generated a staging system for LSV on the basis of number of the "echogenic stripes [6, 29]. Although, this classification might be useful, the echogenicity and the thickness of the linear stripes were not included. More recently, Hong et al. measured the diameter of the affected vessel and used 2.5 mm as the cutoff for stage mild vs. severe LSV, but it was unclear why 2.5 mm was used as cutoff [30]. Nonetheless, the pattern of LSV recognition was retrospective without validation in all of these studies and there were no serial cUS analyzed to examine progression. The diagnosis of LSV can be operator dependent, suggesting that the current definitions of LSV may be inadequate in light of the advanced cUS technology.

Therefore, we developed a new classification for LSV transitioning from faint visibility to increased echogenicity and to increased echogenicity plus thickness to reflect our observations for "developing vasculopathy". Importantly, we confirmed that the diagnostic agreement for LSV on cUS among a group of pediatric radiologists significantly improved after establishing the new classification. We strongly suspect that the lack of uniform diagnostic criteria has been a major contributor to the variability of the diagnosis among radiologists, which likely confounded the true incidence of LSV.

Hypoxic/ischemic conditions are reported to be the leading cause of LSV in several retrospective cohort studies and case series [8, 9, 18, 21, 31, 32]. However, case–control studies have failed to show a significant association between hypoxic/ischemic conditions and LSV [7, 19, 22, 23, 28]. In a recent retrospective case–control study, it was observed that isolated late onset LSV (seen on cUS > 5d postnatal) was associated with younger GA, lower BW and the presence of BPD [33]. We also observed that BPD was associated with the occurrence of LSV, but found no relation with GA or BW. However, BPD and NEC, which are associated with systemic inflammatory responses, were associated with the progression of LSV in the postnatal period. This could relate to the neutrophil and macrophage influx as well as increased levels and expression of pro-inflammatory cytokines such as IL-8, TNFα, IL-1, and IL-6 found in the tracheal aspirates of neonates who subsequently developed BPD [34–37]. Similarly, histological sections of intestine from preterm infants with NEC show ischemia with inflammation [38], which is associated with increased levels of circulating cytokines [39, 40]. It is notable that the smaller deep penetrating arteries of the brain are particularly susceptible to hypoxic-ischemic injury [41, 42] and infection [3]. Thus, inflammation may represent a common pathway to the development and progression of vasculitis in the lenticulostriate arteries, explaining the deposition of granular, basophilic material on

histopathology that was previously described in the brains of neonates with LSV [2, 8, 9].

Robust evidence now exists that non-infections causes of LSV may be more common than congenital infections [7, 8, 18, 21, 32]. In earlier reports there was an association between LSV and congenital infection, in particular CMV [1, 2, 4, 43–46]. More recently, this has been questioned [7, 32, 33]. We obtained urine CMV cultures from 98% of the neonates with LSV at the time of diagnosis, but only one neonate tested positive for congenital CMV infection. This occurred in a 32wks GA neonate who had Stage 3 LSV on the first cUS obtained at 7d postnatal and remained Stage 3 throughout the hospitalization. Thus, congenital infection may account for some cases, but this may be far fewer than originally thought.

Whether or not LSV progresses after birth remains unclear, and if so, the variables associated with its progression are unclear. In earlier reports it was suggested that LSV appeared shortly after birth and persisted without evidence of progression or resolution; however, most of these neonates were born at term [4, 5, 9]. Progressive postnatal changes of LSV have been observed in neonates with pulmonary and cardiac diseases [8]. We observed that neonates with LSV on cUS <15d postnatal were more likely to present with Stages 2 and 3 on their initial cUS. This is in contrast to LSV first seen >15d postnatal, when it was more likely to be Stage 1. Only 2/65 neonates showed resolution of LSV by discharge. Of note, neonates who progressed from Stage 0 to 3 LSV were more likely to have evidence of hypothyroidism, which is similar to the observations of Chamnanvanakij et al. in our hospital 18 yrs ago [22]. Both of the neonates that progressed to Stage 3 and had hypothyroidism also had developed BPD. Since only seven neonates progressed to Stage 3, this will require confirmation.

Few investigators have examined the developmental outcome of preterm neonates with LSV. In a recent systematic analysis [47] of long-term outcomes of preterm neonates with LSV, it was concluded that the current literature contained insufficient data to make conclusions since the majority of reports were small, retrospective and contained conflicting conclusions [13, 22, 30]. Further, these studies did not exclude preterm neonates with other intracranial pathology, e.g., ICH and PVL. In the present study, NDI in infants with LSV and no other pathology on cUS did not differ from control infants at 18–36mon. They also did not differ from neonates who had other findings on cUS. Thus, the presence of LSV, regardless of the stage, does not portend to worse NDI after correction for GA at birth.

Strengths of this study include its prospective design and effort to reduce the inter-rater variability by designing and validating a new classification system for LSV. The new classification not only improved inter-rater reliability of the diagnosis of LSV on cUS, but also allowed us to define how LSV evolves after birth and to examine the clinical risk factors associated with its progression. The limitation of our study was that our follow-up rate was only 67% for both infants with LSV and their control group. However, the fact that infants with LSV who completed the follow-up were smaller, younger, and clinically similar to those who were not seen at follow-up could partially mitigate this limitation.

In conclusion, LSV appears to occur in 15% of the preterm infants <32wks GA after implementing a valid and reproducible classification that can be used by the pediatric radiologists. Importantly, LSV may no longer be primarily associated with congenital CMV or other infections, but rather with the development of inflammatory processes; but this will require further study. Finally, we have shown that LSV in the absence of other intracranial pathology is not associated with an increased risk for adverse neurodevelopmental outcomes in preterm infants <32wks GA.

Author contributions JS: Wrote the first draft of the manuscript. She conceptualized and designed the study. She collected and reviewed data from the database, medical records, participated in the interpretation of the data, critically reviewed revisions, and approved the final manuscript. LC: Conceptualized and designed the study. She participated in the interpretation of the data, critically reviewed and approved the manuscript. RH: Conceptualized and designed the study. He participated in the interpretation of the data, follow-up data review and abstraction, critically reviewed and approved the manuscript. MP: Conceptualized and designed the study. She reviewed and classified all the ultrasonograms, without knowledge of prior readings and outcome and participated in data interpretation and critically reviewed the manuscript. DW: Conceptualized and designed the study. She reviewed and classified all the ultrasonograms without knowledge of prior readings and outcome and participated in data interpretation and critically reviewed the manuscript. SB: Conceptualized and designed the study. He completed all statistical analyses, participated in the interpretation of the data, and critically reviewed the manuscript. CR: Conceptualized and designed the study. He participated in the interpretation of the data and critically reviewed, revised and approved the final manuscript.

Compliance with ethical standards

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