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Lenticulostriate vasculopathy in extremely low gestational age newborns: Inter-rater variability of cranial ultrasound readings, antecedents and postnatal characteristics

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Abstract

Although lenticulostriate vasculopathy (LSV) was first detected on a cranial ultrasound nearly 30 years ago, its clinical implications and significance remain unknown. The objective of this study was to evaluate the inter-rater reliability of cranial ultrasound readings of LSV, and to explore relationships with potential antecedents and developmental correlates in extremely low gestational age newborns. Of the 1506 infants enrolled during the years 2002–2004, 1450 had at least one set of ultrasound scans evaluated for LSV and 939 had all three sets. To evaluate the inter-rater agreement for identifying LSV, we compared readings from two independent radiologists on days 1–4, 5–14, and on or after day 15. We then evaluated the relationships between LSV and maternal, antenatal, and postnatal characteristics. Our results showed that kappa values were 0.18, 0.33, and 0.36 on days 1–4, days 5–14, and day 15 or greater. Infants who were identified as LSV positive by two readers had higher Score for Neonatal Acute Physiology-II (an illness severity indicator), higher rates of tracheal infection and bacteremia, lower partial pressure of arterial oxygen and pH levels on 2 of the first 3 postnatal days, and they were more likely to have a lower psycho-motor development index at age 2 years. Positive agreement on the presence of LSV was low, as was the

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kappa value, an index of inter-rater reliability. Infants with high illness severity scores and their correlates were at increased risk of developing LSV, while those who develop LSV appear to be at increased risk of motor dysfunction.

Keywords

Lenticulostriate vasculopathy; cranial ultrasound; thalamus; basal ganglia

1. Introduction

When lenticulostriate vasculopathy (LSV) was first identified on a cranial ultrasound in 1985, these hy-perechogenic lines seen in the basal ganglia and/or thalamus accompanied calcifications in infants who had a congenital TORCH (*Toxoplasma gondii*, Other, Rubella, Cytomegalovirus and Herpes viruses) infection [1]. Support for the concept that LSV is a vas-culopathy comes from Doppler studies [2–5] and from post-mortem reports of thickened, hypercellular arterial walls, and intramural or perivascular basophilic deposits in the basal ganglia and/or thalamic regions of newborns who died with LSV [6–8]. These lesions were found in only about half the children whose brain was examined histologically [6–10], prompting the inference that some children with the LSV ultrasound signature do not have a vasculopathy.

Most published reports of LSV are retrospective reviews [3,7,9–12] or case reports [1,2,6,13–17], with the diagnosis frequently made by only one reader. Further, prospective studies of LSV are limited in number, sample size, and quality, and have produced conflicting results [8,18–20]. In light of these limitations, the associated risk factors and clinical relevance of LSV identified on cranial ultrasound remain unclear.

There were 1450 sets of cranial ultrasound scans in the extremely low gestational age newborn (ELGAN). Study database provided an opportunity to correct some of these deficiencies. We evaluated the inter-rater reliability of identifying linear or punctate hyperechoic lesions in basal ganglia and/or thalami, the sonographic criteria for LSV. We also evaluated the relationships between LSV and pregnancy, maternal, placental, neonatal, and developmental characteristics in ELGANs, defined as those born before the 28th wk of gestation.

2. Materials and methods

The ELGAN study was designed to identify characteristics and exposures that increase the risk of structural and functional neurologic disorders in ELGANs. During the years 2002–2004, women delivering before 28 wk gestational age were asked to enroll in the study [21]. The enrollment and consent procedures were approved by the individual institutional review boards. The subjects for this report are the 1450 ELGANs who had at least one set of ultrasound scans read for LSV.

2.1. Demographic, pregnancy and delivery variables

The clinical circumstances that led to each maternal admission and ultimately to each preterm delivery were defined operationally using data from a maternal interview and data abstracted from the medical record [22].

2.2. Newborn variables

Gestational age 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 the 14th wk (62%). When these were not available, reliance was placed sequentially on a fetal ultrasound at 14 or more wk (29%), LMP without fetal ultrasound (7%), or the gestational age recorded in the log of neonatal intensive care unit (1%). The birth weight Z-score represent the number of standard deviations the infant's weight is above or below the mean of infants at the same gestational age in a standard data set [23].

We collected physiology, laboratory and treatment data for the first 12 postnatal hours needed to calculate a Score for Neonatal Acute Physiology (SNAP-II™) [24–26]. Mode of ventilation was defined as the highest level of support on day 7. We classified ELGANs by their extreme blood gas measurements on postnatal days 1, 2, and 3 [27]. For each of these days we had the lowest and the highest partial pressure of arterial oxygen (PaO_2), partial pressure of carbon dioxide, and pH. In our sample, the blood gas measurement that defined the extreme quartile varied by gestational age and by postnatal day. Consequently, we classified infant by whether or not their extreme value each day was in the extreme quartile for their gestational age (23–24, 25–26, and 27 wk). Because an extreme measure on 1 day could reflect a fleeting event, we required that an infant be in the extreme quartile on at least 2 of the 3 days to be considered 'exposed' to such extremes.

Documented early bacteremia was defined as recovery of an organism from blood drawn during the first week, and late bacteremia was defined as recovery of an organism from blood drawn during weeks 2, 3, or 4 [28,29].

2.3. Placentas

Each delivered placenta was placed in a sterile exam basin and transported to a sampling room. Eighty two percent of the samples were obtained within 1 hr of delivery. The microbiologic and histo-logic procedures are described in detail elsewhere [30–33].

2.4. Protocol ultrasound scans

Routine scans were performed by technicians at all the hospitals using high frequency transducers (7.5 and 10 MHz). Ultrasound studies always included the six standard quasi-coronal views and five sagittal views using anterior fontanel as the sonographic window [34].

Of the 1450 infants who had at least one set of protocol ultrasound scans, 939 had all three sets. Protocol one scans were obtained between the 1st and 4th day (n = 1133): protocol two

scans were obtained between the 5th and 14th day (n = 1340): and protocol three scans were obtained between the 15th day and the 40th wk (n = 1246).

All ultrasound scans were interpreted by two independent sonologists who were not provided clinical information [35]. Each set of scans was first interpreted by a study sonologist at the infant's birth institution. The images, usually as electronic images embedded in the software eFilm workstation™ (Merge Healthcare/Merge eMed, Milwaukee, WI) copied to a CD, were then sent to a second sonologist at another ELGAN study institution for a second, independent interpretation. The eFilm program allowed the second reader to see what the first reader saw, and provided options to adjust and enhance the images, including the ability to zoom and alter image contrast and brightness. When the two readers differed in their recognition of intraventricular hemorrhage, moderate/severe ventriculomegaly, hyperechoic (echo-rich, echogenic) lesion, or hypoechoic (echo-poor, echolucent) lesion, the films were sent to a third (tie-breaking) reader who did not know what the other readers reported.

We considered a child to have LSV if linear or punctate hyperechoic lesions were identified in the basal ganglia and/or thalami. Because identification of LSV was not a primary aim of the ELGAN study, studies that were interpreted discrepantly as to the presence of LSV were not evaluated by a third reader.

We defined an LSV diagnosis for each infant:

- **a.** LSV negative: Both readers agreed LSV was absent on all available sets of scans.
- **b.** LSV positive, two readers: There was consensus on the presence of LSV on at least one or more sets of scans.
- **c.** LSV positive, one reader: There was no consensus on the presence of LSV on any set of scans. Only one of the two readers identified LSV on one or more set.

2.5. 24 mo developmental assessment

Families were invited to bring their child for a developmental assessment close to the time when s/he would be 24 mo corrected age. The full evaluation included a neurological examination and the Bayley Scales of Infant Development, Second edition (BSID-II) [36]. The head circumference was measured as the largest possible occipital-frontal circumference. Measurements were rounded to the closest 0.1 cm. All head circumferences were converted to Z-scores because children were seen at different approximations of 24 mo corrected age (range: 16–44 mo corrected age, with 68% assessed between 23–25 wk corrected age). Z-scores were based on standards in the centers for disease control and prevention data sets [37].

All neurological examiners trained to minimize examiner variability, and demonstrated acceptably low variability [38]. The topographic diagnosis of cerebral palsy (quadriparesis, diparesis, or hemipare-sis) was based on an algorithm using ELGAN study data [35].

Certified examiners administered and scored both the mental developmental index and psychomotor developmental index of the BSID-II, adjusting for age as appropriate. A score

of <55 placed the child more than three standard deviations below the expected mean, while a score between 55 and 69 placed the child more than between two and three standard deviations below the expected mean.

2.6. Data analysis

We first sought to evaluate inter-rater variability of identifying LSV on each of the three ultrasound scans. Inter-rater reliability between the readers was assessed by using kappa statistics. Kappa measures the strength of the agreement beyond what would be expected by chance alone. Kappa > 60% generally is considered to be 'good', and > 80% is considered to be 'excellent' [39].

We then evaluated relationships between the LSV diagnosis groups and pregnancy, placenta, delivery, and neonatal characteristics and exposures, and developmental characteristics at age 2 yr. In light of the small number of children classified as LSV positive, two readers (n = 33), we did not try to test any hypotheses about relationships between antecedents and LSV or between LSV and development at 2 yr. The assessments we carried out should be viewed as exercises in hypothesis generation.

3. Results

3.1. Inter-rater reliability of cranial ultrasound scans (Table 1)

Of the 1450 infants whose cranial ultrasound scans were evaluated for LSV, both readers agreed that LSV was present in sets of scans from 33 infants (2.3%). Readers had disagreement on 110 infants, where only one of the readers reported the presence of LSV (7.6%). Finally, both readers agreed that LSV was not present in sets of scans from 1307 infants.

Of the 1133 protocol scans obtained on days 1–4, 10 were read as positive for LSV (0.9%). Of these, nine were read as positive by one reader while the two readers agreed upon the presence of LSV in only one scan. The readers agreed that LSV was absent in 1123 scans. Positive agreement was 18% and negative agreement was 99.6% for a kappa of 0.18 (95% confidence interval [CI]: 0.13–0.48).

The prevalence of any LSV was 2.2% among the 1340 protocol scans obtained on days 5–14. Only six of the 29 scans were read as positive for the presence of LSV by both readers. The two readers agreed that LSV was absent on 1311 scans. Positive agreement was 34%, negative agreement was 99%, and the kappa was 0.33 (95% CI: 0.13–0.53).

Of the 1246 protocol scans obtained on or after day 15, 120 scans were read positive for presence of LSV (9.6%). Of the 60 scans obtained after the 36th post-natal wk, four (6.7%) had LSV according to one or both of the readers. Only 30 of these 120 scans were read as positive by two readers. They agreed that LSV was absent in 1126 scans. Positive agreement was 40%, and negative agreement was 96%, yielding a kappa value of 0.36 (95% CI: 0.25–0.46).

3.2. Association of LSV on any scan with other ultrasound lesions (Table 2)

Infants identified as LSV positive by two readers on any scan were less likely than others to have intra-ventricular hemorrhage or ventriculomegaly (12% *vs.* 25%/23% and 3% *vs.* 13%/6%), but were more likely to have a white matter hypoechoic lesion (12% *vs.* 8%/6%). Infants with LSV, whether identified by only one reader or by two, tended to have higher rates of a white matter hyperechoic lesion than the infants without LSV (21%/22% *vs.* 16%).

3.3. Demographic characteristics (Table 3 and supplement Tables A–C)

Infants identified as LSV positive by two readers were more likely than others to have been born to a woman who had public insurance (55% *vs.* 41%/ 40%) and to be from a multiple gestation pregnancy (42% *vs.* 33%/25%). These infants were less likely to have been exposed to a complete course of antenatal steroids (48% *vs.* 63%/65%), and to have a very low birth weight Z-score (3% *vs.* 8%, at least compared to LSV negative infants). They did not differ appreciably from others in race, pregnancy complications, exposure to magnesium sulfate, cesarean delivery, gestational age, birth weight or placenta histology. On the other hand, the placentas of infants who had LSV according to two readers were more likely than the placentas of others to harbor multiple organisms, an aerobe, a vaginal organism and/or a skin organism.

3.4. Early postnatal characteristics (Table 4)

Compared to others, infants identified as LSV positive by two readers tended to have a high SNAP-II (≥ 30 within the first 12 hr after birth) (42% *vs.* 26%), a documented tracheal infection (39% *vs.* 21%/29%), bacteremia (early: 15% *vs.* 6%: late: 54% *vs.* 25%/ 34%), and a PaO_2 (35% *vs.* 22%/25%) and a pH (35% *vs.* 21%/26%) in the lowest quartile on 2 of the first 3 postnatal days.

3.5. Developmental assessment at age 2 yr (Table 5)

Children who had LSV according to two readers were more likely than others to have diparetic cerebral palsy (10% *vs.* 3%) and a psychomotor development index more than two standard deviations below the expected mean (45% *vs.* 31% and 27%).

4. Discussion

4.1. Incidence of LSV

In this study of 1450 infants born before the 28^{th} wk of gestation, 2.3% had LSV identified by two readers, while an additional 7.6% had LSV identified by one of two readers on one or more protocol ultrasound scans. Our 2.3% incidence of LSV (identified by two readers) is in agreement with earlier reports of 0.3–5.8% [3,6–12,18,19]. However, more recent studies reported higher incidences of 10–31.6% [20,40,41]. The apparently increasing incidence reported in the literature might reflect nothing more than a growing awareness of this disorder. On the other hand, alternative explanations deserve consideration. For example, improved ultrasound imaging might contribute, as might increased frequency of risk factors that contribute to a truly increased incidence of LSV.

A recent prospective study, in which all the cranial ultrasounds in the neonatal intensive care unit (NICU) were evaluated for LSV found that, LSV occurred only 5% of infants born before the 30th wk of gestation, whereas it occurred in 66% of the infants who were born after the 33rd wk but before term, and 28% were born at term [19]. These figures need to be interpreted with great caution because of the increasing selection with increasing gestational age of who gets admitted to the NICU. All ELGANs are admitted to the NICU, but only the sickest term-born infants are admitted to a level III NICU.

4.2. Inter-rater reliability

Inter-rater reliability of common intracranial lesions in premature infants appears to be high for ven-triculomegaly, intracranial hemorrhage and hy-poechoic lesions, and low for hyperechoic lesions [35]. To our knowledge, our study is the first study that investigated the inter-rater reliability of a LSV diagnosis. Among radiologists who have expertise in neonatal disorders, the positive agreement for LSV was low as was the kappa value, an index of inter-rater agreement (Table 1). Because diagnostic confidence is enhanced by consensus readings [42,43] we recommend that future studies of LSV, engage in exercises to reduce observer variability and employ multiple readers, reading together or independently.

4.3. The timing of the lesion

In term infants, LSV tends to occur soon after birth [1,6,8,9]. In preterm newborns, however, LSV appears to evolve over the first few postnatal weeks [8,44], a finding we can confirm. Our data suggest that in extremely premature infants, LSV tends to become evident after the 2nd postnatal week. Two studies separated LSV patients into two groups based on the first detection of the lesion, before or after 7–10 days [12,20]. Both reported that infants who develop LSV early were more mature than the infants in the late-onset LSV group, a finding we can not confirm.

4.4. Antecedents

Our finding that the placentas of infants with LSV were more likely than those of infants without LSV to harbor organisms raises the possibility that antenatal inflammatory phenomena contribute to the occurrence of LSV in very preterm newborns. On the other hand, we did not find that histologic inflammation of the placenta was associated with LSV. We have confidence in our bacteriology, in part because the recovery of low virulence microorganisms from the placenta without histologic inflammation predicted cerebral white matter injury and cerebral palsy in this population of ELGANs [45].

In our study, infants with LSV identified by two readers were less likely than others to have been exposed to a complete course of antenatal steroids. This inverse relationship was found in one study of preterm infants born at less than 35 wk [12], but was not found in two studies of preterm infants born at less than 32 and 34 wk [20,40]. Thus, if steroids prevent LSV, they probably do so rather ineffectively.

Infants with LSV identified by two readers were more likely than their peers to have a high SNAP-II, harbored bacterium in a tracheal aspirate and/or blood, and PaO_2 and a pH in the lowest quartile for gestational age on 2 of the first 3 postnatal days. In essence, LSV is most

often found in the sickest newborns, who are often the ones most likely to have tracheitis, bac-teremia, hypoxemia, and acidemia. What makes some of them vulnerable to LSV remains unclear.

4.5. Putative consequences

Children identified by two readers as having LSV were more likely than others to have a low psycho-motor development index. This finding is comparable to that of one other study of the development of children with LSV [12]. In that study, 15 children with LSV were more likely than their 19 children peers without LSV to have abnormal tone (not defined) at age 6 mo (33% *vs.* 5%).

We did not find that LSV children differed from others in rates of a low mental development index (29% *vs.* 27%), while the other study found that LSV children were more likely than others to have had an abnormal Denver development assessment (20% *vs.* 10%).

4.6. Strengths and limitations

The strengths of our study include the use of prospectively collected data from a large multi-center cohort of preterm newborns. Our patients were exclusively ELGANs, and our study represents the largest sample of such preterm infants in the literature. In addition, all of the sonologists are highly experienced and worked together to reduce observer variability in assessments of other lesions.

To reduce observer variability of the lesions that were of primary interest to the investigators and sonologists, the ELGAN study had a manual that provided instructions about what all agreed was deemed worthy of identification. Sonologists also shared scans that posed diagnostic problems and held conference calls to achieve consensus about what constituted each lesion. This was not done for LSV. We consider the lack of these efforts to reduce observer variability to be the major limitation of our study.

With only 33 children classified as LSV positive by two readers, our study has limited power. As with all observational studies, our findings allow us to draw inferences about associations but not causation.

In conclusion, LSV appears to occur in at least 2% of ELGANs, and is usually first evident after the second postnatal week. Most of the newborn’s characteristics and postnatal exposures associated with LSV lead to the inference that the sickest infants are at highest risk for developing LSV and that those who developed LSV are at heightened risk of motor dysfunction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

The number of scans read by two sonologists, independently, for the presence or absence of len-ticulostriate vasculopathy, and the percentage of scans that were positive and negative for agreement, with kappa values, for days 1 to 4, 5 to 14, and 15 and later

	Scan on days 1 to 4		Scan on days 5 to 14		Scan on days 15 or later	
	First reader					
Second reader	Positive	Negative	Positive	Negative	Positive	Negative
Positive	01	4	06	13	30	41
Negative	05	1123	10	1311	49	1126
Positive agreement (%)	18		34		40	
Negative agreement (%)		99.6		99		96
Kappa	0.18		0.33		0.36	

Table 2

Percent of children with each consensus-classified LSV diagnosis who had the cranial ultrasound lesion identified on the left (These are column percents)

Cranial ultrasound lesion	Reading of LSV			Row *n*
	LSV negative 2 readers	LSV positive 2 readers	LSV positive 1 readers*	
Lateral ventricles				
Intraventricular hemorrhage	25	12	23	351
Moderate/severe enlargement	13	03	06	172
Cerebral white matter				
Hyperechoic lesion(s)	16	21	22	235
Hypoechoic lesion(s)	08	12	06	113
Maximum number of infants	1307	33	110	1450

* One reader, but not both, said LSV present.

LSV = Lenticulostriate vasculopathy.

Table 3

Percent of children with each consensus-classified LSV diagnosis who had the demographic or pregnancy characteristics identified on the left (These are column percents)

Demographic or pregnancy characteristics	Lenticulostriate vasculopathy			Row *n*
	LSV negative 2 readers	LSV positive 2 readers	LSV positive 1 reader*	
Race				
White	58	58	57	827
Black	29	36	32	415
Other	13	6	10	182
Public insurance				
Yes	41	55	40	579
Antenatal corticosteroid				
Complete	63	48	65	904
Partial	26	39	26	382
None	11	12	09	159
Pregnancy complication				
Preeclampsia/fetal indications	18	15	15	263
$MgSO_4$				
None	33	31	35	478
Tocolysis	54	56	53	781
Seizure	13	13	12	179
Cesarean delivery				
Yes	66	64	58	943
Multiple gestation				
Yes	33	42	25	473
Gestational age (wk)				
23–24	26	24	26	377
25–26	44	55	47	640
27	30	21	26	433
Birth weight (g)				
750	43	42	40	620
751–1000	39	48	48	577
1000	18	9	12	253
Birth weight Z-score				
< −2	08	03	03	104
≥ −2, < −1	14	15	16	205
≥ −1	78	82	81	1141
Maximum number of infants	1307	33	110	1450

*One reader, but not both, said LSV present.

LSV= Lenticulostriate vasculopathy.

Table 4

The percent of children with each consensus-classified LSV diagnosis who had the early postnatal characteristic listed on the left (These are column percents)

Postnatal factors	LSV			Row *n*
	LSV negative 2 readers	LSV positive 2 readers	LSV positive 1 reader*	
Score for neonatal acute physiology-II (0–12 hr)				
20	49	36	52	697
20–29	25	21	22	348
30	26	42	26	381
Tracheal infection				
Definite	21	39	29	308
Early bacteremia				
Definite	06	15	06	90
Late bacteremia				
Definite	25	54	34	362
Mechanic ventilation, day 7				
Yes	64	64	62	903
lowest Q PaO2**				
Yes	22	35	25	258
Highest Q PaO2**				
Yes	21	12	21	246
lowest Q PCO2**				
Yes	22	12	26	259
Highest Q PCO2**				
Yes	22	23	25	256
Lowest Q pH**				
Yes	21	35	26	254
Maximum number of infants	1307	33	110	1450

*One reader, but not both, said LSV present.

**Extreme quartile for gestational age on two of the first three postnatal days.

LSV= Lenticulostriate vasculopathy.

Table 5

The percent of children with each consensus-classified LSV diagnosis who also had the characteristic on the left at age 2 yr (These are column percents)

Postnatal factors	LSV			Row *n*
	LSV negative 2 readers	LSV positive 2 readers	LSV positive 1 reader*	
Cerebral palsy diagnosis				
Quadriparesis	06	00	05	64
Diplegic	03	10	03	37
Hemiparesis	02	00	03	19
Bayley scales of infant development				
Mental developmental index < 70	27	29	22	269
Psychomotor developmental index < 70	31	45	27	314
Head circumference (Z-score)				
< −2	10	06	10	107
≥ −2, < −1	18	23	22	193
Maximum number of children	941	31	79	1051

*One reader, but not both, said LSV present.

LSV= Lenticulostriate vasculopathy.