Imaging the preterm infant's brain

Leijser, L.M.

Chapter 12

Lenticulostriate vasculopathy in very preterm infants

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Abstract

Background and Aim:
Lenticulostriate vasculopathy (LSV) can be seen on neonatal cranial ultrasound (cUS) scans and has been associated with various clinical conditions. Studies in preterm infants are limited. Our aim was to assess for LSV on cUS of very preterm infants: incidence and aetiology, evolution during neonatal period, association with clinical parameters, and magnetic resonance imaging (MRI-)equivalent.

Patients and Methods:
Very preterm infants (< 32 weeks), admitted to our tertiary neonatal referral centre, underwent sequential cUS throughout the neonatal period and MRI around term age. cUS were evaluated for LSV and other changes, and MRI for changes in signal and myelination in deep grey matter. LSV was divided in early-onset (≤ 7 postnatal days) and late-onset (> 7 postnatal days). Perinatal clinical parameters were collected for all infants and compared between groups.

Results:
In 22 out of 111 (20%) infants LSV was detected: early-onset in five and late-onset in 17. LSV mostly presented some weeks after birth and persisted for several months. There were no associations between LSV and other changes on cUS or deep grey matter changes on MRI. Infants with late-onset LSV were younger and smaller at birth than infants with early-onset LSV. Postmenstrual age at first detection was comparable for both LSV groups. There were no associations between LSV and perinatal clinical parameters, but infants with LSV had less episodes of hypotension than infants without LSV.

Conclusions:
LSV is a frequent finding on cUS in very preterm infants, but does not show on MRI. The postmenstrual age, rather than gestational and postnatal age, seems important in LSV development. LSV is not associated with clinical parameters. When encountered in otherwise healthy preterm infants, LSV is probably a benign temporary phenomenon.

Introduction

Lenticulostriate vasculopathy (LSV), presenting as hyperechogenic vessels in the basal ganglia and/or thalamus (BGT) region, can be detected on cranial ultrasound (cUS) scans of neonates (1). The incidence of LSV in neonates varies between 0.3-32% (2-16). LSV can be unilateral or bilateral, and punctate, linear or branching (4-5,9-10,17). Histological studies show intramural and perivascular depositions of amorphous basophilic material in the lenticulostriate vessels, probably causing the hyperechogenic appearance on cUS. The vessels are usually medium sized, having thickened and hypercellular walls without fibrosis or hyalinisation (2,5,9,13).

LSV has been associated with several clinical conditions, including infections, both congenital (e.g. Toxoplasmosis, Other, Rubella, Cytomegalovirus, Herpes (including Parvo B19) (TORCH) infections) and acquired, chromosomal abnormalities, congenital heart disease, other congenital malformations, hypoxic-ischaemic events, fetal alcohol and drug exposure, twin-to-twin transfusion syndrome, neonatal lupus erythematosus, hydrops fetalis, metabolic disorders and diabetic fetopathy (2-10,12-13,15,17-28). It occurs more often in infants of multiple than of singleton pregnancies and in full-term than in preterm neonates (12-13,25-26). However, the aetiology and clinical significance of LSV are largely unclear (8,13,15).

Prospective studies on the incidence and aetiology of LSV and associated clinical parameters in preterm infants are limited (4-5,10,12,14-15). The aims of our prospective study were to assess the incidence, aetiology and evolution of LSV in a large cohort of very preterm infants. Additional aims were to assess its association with various perinatal clinical parameters, previously associated with brain injury in preterm infants, presence of an equivalent on magnetic resonance imaging (MRI), and presence of changes in maturation of the BGT in infants with as compared to without LSV.

Patients and Methods

Patients

Very preterm infants (gestational age (GA) < 32 weeks), admitted to the tertiary neonatal unit of the Leiden University Medical Center between May 2006 and October 2007, were eligible for a neuro-imaging study, assessing and comparing brain imaging findings on cUS and MRI. For this part of the study, emphasis was placed on LSV. Ethical approval for the study was given by the Medical Ethics Committee and informed consent from the parents was obtained for each infant. Exclusion criteria were congenital anomalies of the central nervous system, severe other congenital anomalies, chromosomal and metabolic disorders, and neonatal meningitis.

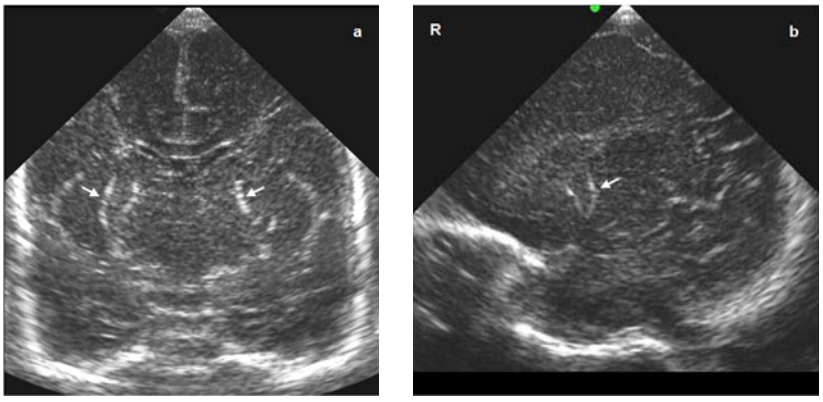
Cranial ultrasound

As part of the routine care, sequential cUS scans were performed by the attending (fellow) neonatologists, using an Aloka α10 scanner with multifrequency transducer (Biomedic Nederland B.V., Almere, the Netherlands), within 24 hours of birth, at least weekly from the day of birth or admission until discharge or transfer to another hospital, and on the day of the term equivalent MRI examination (29). Of included infants, all cUS scans were assessed as recently described (30).

LSV was considered present when on at least one cUS examination, a punctate or linear echogenic structure was seen in the distribution of the thalamo-striatal vessels in the BGT region, on both coronal and (para)sagittal views (Figure 1). The side (left and/or right), appearance (punctate, linear and/or branching), and location (basal ganglia and/or thalamus) were recorded. The day LSV was first detected on sequential cUS and its evolution and duration (up to the day of the term equivalent cUS) were noted. As previous studies described differences between preterm infants with LSV presenting within the first 7-10 days of birth and thereafter (11), we divided LSV into early-onset (first seen on initial or subsequent cUS performed ≤ 7 days of birth) and late-onset (first seen on cUS performed > 7 days of birth).

Other changes, including echodensities in the frontal white matter (frontal echodensities), periventricular echodensities, cystic white matter lesions, intraventricular haemorrhage, post-haemorrhagic ventricular dilatation, and periventricular haemorrhagic infarction, were recorded (30).

Figure 1. Coronal (a) and sagittal (b) cUS scans of a preterm infant (gestational age 26.4 weeks), scanned at postmenstrual age 30.7 weeks, showing bilateral lenticulostriate vasculopathy having a branching appearance on the right side and a linear appearance on the left side.



MRI

MRI examinations were performed in all very preterm infants, preferably around or just after term equivalent age (TEA), according to our standard protocol, using a 3 Tesla Philips MR system (Philips Medical Systems, Best, the Netherlands) as recently described (31). For infants who were still unstable and/or ventilator dependent around that age, MRI was postponed. For this part of the neuro-imaging study, only the T_1-, T_2-, and susceptibility-weighted sequences were analyzed.

All MRIs were assessed as recently described (30). Special attention was paid to signal intensity changes in the BGT. The side (left and/or right), appearance, and location (basal ganglia and/or thalamus) were recorded. Myelination in the BGT region was compared to reference images, obtained with lower field strengths (32-35).

Clinical parameters

For all included infants the following perinatal clinical parameters were retrospectively collected: antenatal corticosteroid treatment; GA at birth; birth weight; gender; plurity and in case of monochorionic twins presence of twin-to-twin transfusion syndrome; congenital TORCH infection based on positive maternal serum IgM or PCR screening; respiratory distress syndrome requiring mechanical ventilation and surfactant treatment; bronchopulmonary dysplasia, if oxygen dependence ≥ 30% at 36 weeks'

postmenstrual age (PMA) (36); dexamethasone treatment for bronchopulmonary dysplasia; patent ductus arteriosus requiring medical and/or surgical treatment; hypotension requiring inotropic treatment; sepsis, if positive blood culture, and/or necrotizing enterocolitis, if grade ≥ 2a according to Bell et al. (37).

Data analysis

Statistical analyses were performed using SPSS software (version 14.0; SPSS inc., Chicago, Illinois, USA). For the analyses, only infants who were admitted to our unit for at least 7 days were included. The incidence of LSV was calculated. Incidences of (other) changes on cUS and MRI were compared between infants with and without LSV, using a Pearson χ^2 test. Subsequently, infants with LSV were divided into early-onset and late-onset groups. Characteristics of LSV and incidences of (other) changes on cUS and MRI were compared between both LSV groups, using a Pearson χ^2 test.

Incidences of clinical parameters were compared between infants with and without LSV and between the early-onset and late-onset groups, using a Pearson χ^2 test for categorical and an unpaired t-test for continuous variables. Clinical variables with $p < 0.1$ were entered into a stepwise logistic regression model to identify independent predictors of LSV. As several of the collected clinical parameters may be strongly related to GA at birth, this was always included in the model. Level of significance was $p \leq 0.05$.

Results

Patients

During the study-period, 182 very preterm infants were eligible for the LSV study, of whom 130 (80 male) were included. Fifty-two infants were excluded; three because of structural brain abnormalities and 49 because informed parental consent was not obtained. Reasons for not obtaining consent included transfer to another hospital or death within a very short period of birth, rejection of participation by the parents, and practical problems such as language barrier and travel distance to the hospital. Median GA and birth weight of included infants were 29.0 (range 25.6-31.9) weeks and 1141 (520-1960) grams, respectively. There were no significant differences in GA and weight at birth between infants with and without informed consent.

In 111 (83.5%; 68 male) infants, sequential cUS (median number 8, range 4-21) were performed during a period of at least 7 days, but in 12 of these infants no or inadequate cUS and/or MRI around TEA were obtained. In three infants, MRI was performed elsewhere, using different protocols. In two infants MR images were difficult to interpret due to movement artefacts, and in seven infants the parents withdrew participation from MRI. Therefore, in 99 infants (61 male) contemporaneous cUS and MRI were obtained at a median PMA of 43.4 (40.1-55.9) weeks. In 61 infants MRI was performed around TEA; in the other 38 between 44.0 and 55.9 weeks' PMA.

Cranial ultrasound (n=111)

LSV

LSV group

In 22 infants (19.8%; 11 male), LSV was detected on at least one cUS examination (median number 6, range 1-12). Median GA and birth weight were 27.9 (26.0-31.7) weeks and 1095 (620-1800) grams, respectively. Characteristics of LSV are shown in Table 1.

Early-onset and late-onset LSV

LSV was detected within the first 7 postnatal days in five infants (22.7%), while thereafter in 17 (77.3%). In three infants, LSV was seen on the first cUS scan performed within 24 hours of birth. Characteristics of LSV and differences therein between infants with early- and late-onset LSV are shown in Table 1. PMA at first detection of LSV was not different between both groups. In infants with early-onset LSV, LSV was significantly more often left-sided than in infants with late-onset LSV, in whom LSV was mostly right-sided. No other differences in characteristics were found.

Table 1. Characteristics of lenticulostriate vasculopathy for the lenticulostriate vasculopathy group and for the early-onset and late-onset lenticulostriate vasculopathy groups separately
(LSV, lenticulostriate vasculopathy; n, number of infants; NS, not significant; PMA, postmenstrual age; pn, postnatal)

Characteristics of LSV			LSV group (n=22)	Early-onset LSV group (n=5)	Late-onset LSV group (n=17)	Early-onset versus late-onset p-value
Detection	First, *median* (range)	Pn age (days)	17.0 (0-117)	0.0 (0-7)	20.0 (13-117)	0.034
		PMA (weeks)	30.5 (27.9-44.1)	30.0 (27.9-31.4)	31.0 (28.1-44.1)	NS
	Last, *median* (range)	Pn age (days)	97.0 (14-166)	62.0 (14-166)	106.0 (57-165)	NS
		PMA (weeks)	42.6 (31.9-55.1)	36.7 (31.9-55.1)	42.7 (35.0-50.4)	NS
	Duration (days), *median* (range)		69.5 (1-166)	62.0 (7-166)	71.0 (1-112)	NS
	On first cUS, *n* (%)		3 (13.6)	3 (60.0)	0 (0.0)	0.006
	On term cUS, *n* (%)		15 (68.2)	2 (40.0)	13 (76.5)	NS
At first detection	Laterality, *n* (%)	Unilateral	15 (68.2)	4 (80.0)	11 (64.7)	NS
		Right	11 (73.3)	1 (25.0)	10 (90.9)	0.022
		Left	4 (26.7)	3 (75.0)	1 (9.1)	
		Bilateral	7 (31.8)	1 (20.0)	6 (35.3)	
	Appearance, *n* (%)	Punctate	4 (18.2)	1 (20.0)	3 (17.6)	NS
		Linear	17 (77.3)	4 (80.0)	13 (76.5)	
		Branching	1 (4.5)	0 (0)	1 (5.9)	

Relation with other changes

In most very preterm infants other changes were detected on cUS (30). No association was found between LSV, or first detection of LSV, and other changes on cUS.

MRI (n=99)

In none of the infants with LSV, including infants with LSV seen on contemporaneous cUS, signal intensity changes were detected in corresponding areas on MRI. Myelination in the BGT region was normal in all infants as compared to reference images. No association was found between LSV and changes in signal or myelination in the BGT on MRI.

Relation between LSV and clinical parameters (n=111)

LSV group

Characteristics of perinatal clinical parameters for infants with and without LSV are shown in Table 2. Infants with LSV had significantly less episodes of hypotension than infants without LSV. Hypotension was identified as an independent variable. No differences were found for the other clinical parameters.

Early-onset and late-onset LSV

Characteristics of clinical parameters for the early- and late-onset LSV groups are shown in Table 2. Infants with late-onset LSV had a significantly lower GA and weight at birth than infants with early-onset LSV. Only GA was an independent variable. No differences were found for the other clinical parameters.

Table 2. Characteristics of clinical parameters for the total group, the lenticulostriate vasculopathy group, the non-lenticulostriate vasculopathy group, and the early-onset and late-onset lenticulostriate vasculopathy groups, and comparison of clinical parameters between groups

(*, independent variable; BPD, bronchopulmonary dysplasia; GA, gestational age; LSV, lenticulostriate vasculopathy; n, number; NEC, necrotizing enterocolitis; NS, not significant; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; TORCH, Toxoplasmosis, Other, Rubella, Cytomegalovirus, Herpes (including Parvo B19); TTTS, twin-to-twin transfusion syndrome)

Clinical parameters		Total group (n=111)	LSV group (n=22)	Non-LSV group (n=89)	LSV versus non-LSV group p-value	Early-onset LSV group (n=5)	Late-onset LSV group (n=17)	Early- versus late-onset p-value
Antenatal corticosteroids, *n* (%)		66 (59.5)	16 (72.7)	50 (56.2)	NS	5 (100)	11 (64.7)	NS
GA (weeks), *median* (range)		28.7 (25.6-31.9)	27.9 (26.0-31.7)	29.0 (25.6-31.9)	NS	29.9 (27.9-31.4)	27.3 (26.0-31.7)	0.041*
Birth weight (g), *median* (range)		1072 (520-1960)	1095 (620-1800)	1065 (520-1960)	NS	1410 (1066-1750)	1030 (620-1800)	0.045
Male, *n* (%)		68 (61.3)	11 (50.0)	57 (64.0)	NS	2 (40.0)	9 (52.9)	NS
Plurity, *n* (%)	Singleton	74 (66.7)	14 (63.6)	60 (67.4)	NS	2 (40.0)	12 (70.6)	NS
	Twin / triplet	37 (33.3)	8 (36.4)	29 (32.6)		3 (60.0)	5 (29.4)	
Monochrionicity, *n* (%)	Total	9 (24.3)	2 (25.0)	7 (24.1)	NS	1 (33.3)	1 (20.0)	NS
	TTTS	6 (66.7)	2 (100)	4 (57.1)	NS	1 (100)	1 (100)	NS
	Donor / recipient	4 / 2	1 / 1	3 / 1	NS	0 / 1	1 / 0	NS
Congenital TORCH, *n* (%)	Performed	24 (27.9)	10 (45.5)	14 (20.9)	NS	2 (40.0)	8 (88.9)	NS
	Positive	0 (0)	0 (0)	0 (0)	NS	0 (0)	0 (0)	NS
Sepsis / NEC, *n* (%)		51 (45.9)	11 (50.0)	40 (44.9)	NS	2 (40.0)	9 (52.9)	NS
RDS, *n* (%)		61 (55.0)	15 (68.2)	46 (51.7)	NS	4 (80.0)	11 (64.7)	NS
BPD, *n* (%)		5 (4.5)	1 (4.5)	4 (4.5)	NS	1 (20.0)	0 (0)	NS
Postnatal dexamethasone, *n* (%)		16 (14.4)	2 (9.1)	14 (15.7)	NS	0 (0)	2 (11.8)	NS
Hypotension, *n* (%)		37 (33.3)	3 (13.6)	34 (38.2)	0.042*	1 (20.0)	2 (11.8)	NS
PDA, *n* (%)		36 (32.4)	5 (22.7)	31 (34.8)	NS	1 (20.0)	4 (23.5)	NS

Discussion

To our knowledge, this is the first prospective study describing the incidence, evolution and association with clinical parameters of LSV in a large cohort of very preterm infants. Our incidence (20%) is higher than previously reported (3-9,11-16). Chamnanvanakij et al. (8) found an incidence of 5.1% in a small group of preterm infants with birth weight < 1250 grams, and in a retrospective study in preterm infants < 35 weeks' GA, an incidence of 4.6% was reported (11). Possible explanations for our higher incidence may be differences in study-populations and ultrasound techniques. We included only very preterm infants, assessed with sequential cUS over a longer period, up to TEA, and also included infants with a punctate appearance of LSV. Ultrasound equipment and techniques have improved considerably over recent years, resulting in higher image quality and possibly better detection of subtle changes. In a study by Paczko et al. (10) in a group of preterm infants up to 37 weeks' GA with otherwise normal cUS in the first postnatal week, an incidence of 31.6% was described. Higher incidences have been reported in full-term than in preterm neonates, probably explaining their high incidence. As we included a large cohort of unselected infants born very prematurely, assessed with frequent high-quality cUS, our data probably reflect the true incidence of LSV in very preterm infants.

LSV was mostly detected after the first few weeks of birth, and persisted for several months, at least up to TEA. At first detection, LSV was mostly unilateral (mainly right-sided) and linear, but often became bilateral and more complex in appearance on subsequent scans before fading towards TEA. These findings are largely consistent with recent studies, describing a mean postnatal age at first detection of 4 to 5 weeks, and LSV to be mostly unilateral (right-sided) and have a progressive or static appearance (4-9,12-13). We and others do not have an explanation for the right-sided predominance of LSV.

In agreement with previous studies (4,9,11,16), the majority (77%) of our preterm infants had late-onset LSV. Only in studies mainly consisting of full-term neonates, LSV was generally present within the first week of life (7,12-13). These findings further indicate that in preterm infants LSV mostly presents after the first postnatal week(s).

Similar to Hemanchandra et al. (11), we found infants with late-onset LSV to be younger

at birth than those with early-onset LSV. However, despite the differences in GA and postnatal age at first detection of LSV between the early- and late-onset groups, the PMA at first detection was not significantly different. In most infants, LSV was first seen between 30 and 31 weeks' PMA. This may indicate that PMA is an important factor in the development of LSV, rather than GA at birth and postnatal age at first detection, and that the lenticulostriate vessels are most vulnerable or prone for LSV before or around this PMA. This hypothesis is supported by the fact that in full-term neonates LSV mostly presents at birth, while in preterm neonates mostly after several weeks (4,7,9,11-13,16).
LSV has been associated with a variety of perinatal conditions. We found a tendency towards more multiple pregnancies in the early-onset group, being in agreement with several previous studies, reporting LSV to occur more often in infants of multiple pregnancies, particularly monochorionic twin pregnancies (12-13,25-26). As we did not find differences in incidence of monochorionic twins between infants with and without LSV, we cannot confirm this finding.
We did not find an association between LSV and congenital TORCH infection: in all infants, both with and without LSV, in whom TORCH screening was performed, results were negative. Our findings are consistent with recent studies, only occasionally describing TORCH infection in neonates with LSV (7,11,13). Therefore, we do not consider TORCH screening warranted in very preterm infants with LSV, unless there are symptoms suggestive of infection.
The aetiology and clinical significance of LSV remain largely unclear (8,13,15). While initial studies suggested an infectious origin (1-3,19), more recent studies have suggested (a combination of) a variety of infectious and non-infectious origins (6-7,9). In addition, late-onset LSV may be due to a perinatal insult to the developing brain, while early-onset LSV may reflect an in utero insult (11).
Histological studies on changes in thalamo-striatal vessels in infants with LSV reported inconsistent findings, possibly partly due to sampling differences and to different stages of LSV (5,9). Some studies found no (peri)vascular abnormalities in involved vessel walls, while others reported depositions of basophilic material as solitary finding or in combination with iron (mineralisation), diffuse microcalcifications and/or calcium (2-3,5,9,13). LSV was therefore thought to represent a vasculopathy, but its underlying pathogenesis is unclear and several potential pathways have been suggested, including vasculitis, hypoxia-ischaemia, and changes in blood flow.

We only found a significant association between LSV, particularly late-onset, and less episodes of hypotension, and do not have an explanation for this finding. We did not find associations with (other) changes on cUS or MRI, and, as expected, no equivalent was found for LSV on MRI (2-6,13,21-22,28). An explanation for this may be that ultrasound and MR imaging are based on different technologies, making detection of vascular deposits and/or calcifications difficult with MRI. In addition, LSV seems to be of vascular origin and does not represent tissue changes. Therefore, the MRI techniques included in this study may not be sensitive to the changes underlying LSV. Possibly, studies on blood flow in and vasculature of involved vessels, including MR angiography, may elucidate vascular changes resulting from LSV and/or may help to study its origin. Based on our results and recent findings, we suggest that a combination of factors underlies LSV.

We appreciate some limitations of our study. In several infants early transfer limited sequential cUS to the early postnatal period. As in most infants LSV was still seen at discharge, it was not always possible to assess its exact duration, and we may have underestimated its duration in four infants in whom it was no longer detected around TEA. We excluded infants with congenital malformations and chromosomal and/or metabolic disorders. Consequently, we cannot comment on the association between LSV and these disorders, and may have slightly underestimated the incidence of LSV in the general preterm population. Finally, no outcome data are, as yet, available for our study-population. Favourable outcome has been found in infants with isolated LSV (13).

In conclusion, this study shows that LSV is a frequent finding in very preterm infants. It often first presents several weeks after birth and persists for several months. PMA, rather than GA and postnatal age, is an important factor in the development of LSV. The aetiology and clinical significance remain unclear and we did not find associations with perinatal clinical parameters, including congenital infections. Our findings suggest that LSV, when encountered in otherwise healthy preterm infants, may be a benign temporary phenomenon.

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