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Short communication

Lenticulostriatal Vasculopathy – a Marker for Congenital Cytomegalovirus Infection?

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A B S T R A C T

Lenticulostriate vasculopathy (LSV) is an ultrasound (US) visible lesion of the brain, which appears as echogenic streaks or spots in the arteries of thalamus and basal ganglia. LSV has varied etiology. Transfontanelar Color Doppler (TFCD) can easily display lenticulostriatal blood flow and assess: stage I LSV with present flow within echogenic changes and stage II LSV in which the flow disappears, despite a presence of streaks and spots, which at this stage most probably correspond to calcification. The objectives of this study are to determine: (1) Whether there are differences in distribution (unilateral or bilateral) and presence (during first year of age) of TFCD flow between congenital CMV infection positive and negative group of children with LSV; (2) Could US and TFCD findings of LSV be an indication for further investigation of possible congenital CMV infection, because of their variable and often adverse neurodevelopmental outcome? We examined and followed-up 98 infants with LSV. One group (37/98) with congenital CMV infection and second (61/98) negative. All infants had clinical signs of neuromotor delay and ultrasound and TFCD markers of LSV. Our study shows that most of the patients from both groups had TFCD visible flow at the age of 0–4 months. In majority of them in both groups, at the age of 5–8 months, there was no more visible flow. TFCD showed no statistically significant difference among congenital CMV infection positive group and negative group, nor in youngest age period (0–4 months), nor in later course of flow in LSV, unilaterally or bilaterally. Although the LSV presents nonspecific marker for intracranial infection (ICI), all infants presenting with LSV should be evaluated for possible ICI. Thus, the Doppler findings of LSV in infants require a detailed examination, monitoring and follow-up of neuromotor outcome.

Key words: *congenital cytomegalovirus infection, CMV, lenticulostriate vasculopathy, Transfontanelar Color Doppler (TFCD), brain ultrasound (US)*

Introduction

Lenticulostriate vasculopathy (LSV) is an ultrasound (US) visible lesion of the brain, which appears as echogenic streaks or spots in the arteries of thalamus and basal ganglia[1–8]. The lenticulostriate arteries are perforating branches of the middle cerebral arteries (MCA). The MCA area is the most frequent location of neonatal cerebral infarction. Whether there is any association between LSV and neonatal cerebral infarction, it is still unknown. LSV is registered with ultrasound in 0.27 to 2.5% of live-born infants, in 3.2 to 5.1% of premature infants and 1.9 to 5.8% of ill newborns[2–8]. It can be unilateral or bilateral, appear on ultrasound as echoic vertical »strip-like«, branched or dotted shape, and pathohistological examination proved that they correlate with small and medium-sized lenticulostriate arteries[9]. It was first described in the year 1960, after rubella epidemic in Philadelphia[10]. Post mortal histological analysis of infant brain showed signs of vasculitis. For unknown reasons, the pathological lesions were localized exclusively in the arteries of the basal ganglia and thalamus[10]. Grant et al. first described the ultrasound findings of these lesions[11] and after him, Teele performed an ultrasound examination in 4500 children in the Children's Hospital Boston and registered congenital cytomegalovirus (CMV), rubella and syphilis infection and trisomy 13 with no signs of infection[12]. Brain biopsy was done which showed basophilic deposit with mineralization and hypercellularity of small and medium-sized arteries. So, Teele first conclu-

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ded that focal vasculopathy found histologicaly, corresponds to the changes registered on intracranial ultrasound examination[12]. LSV has varied etiology and it can be found in cases of infection, hemorrhage, hypoxic-ischemic encephalopathy, infarction, hypoglycemia, calcification, vascular lesion or chromosomal aberrations, and also it may be registered in healthy children[11–16]. Transfontanelar Color Doppler (TFCD) can easily display lenticulostriatal blood vessels, their localization, size and number, and in the gray scale, using spectral analysis of the systole, diastole, mean velocity and resistance index in the real time, blood flow within them can be shown. On the basis of these findings LSV stage can be assessed: stage I LSV with present flow within echogenic changes and stage II LSV in which the flow disappears, despite a presence of streaks and spots, which at this stage most probably correspond to calcification.

The objectives of this study are to determine:

1. Whether there are differences in distribution (unilateral or bilateral) and presence (during first year of age) of TFCD flow between congenital CMV infection positive and negative group of children with LSV;
2. Could US and TFCD findings of LSV be an indication for further investigation of possible congenital CMV infection, because of their variable and often adverse neurodevelopmental outcome?

Patients and Methods

During the period of 4 years, from 1st January 2003 to 31st December 2006 in 218 infants, referred to our Clinic due to deviant neurodevelopmental milestones with or without perinatal risk factors, ultrasound registered echogenic streaks and spots, unilateral or bilateral, diagnosed as LSV. In all of them, CMV serological test and PCR were performed in the Clinic for Infectious Diseases in order to prove or exclude congenital CMV infection. Of these 218 children, 56 children were positive for congenital CMV infection (25.7%), and 162 negative (74.3%). In 37 of 56 children positive on congenital CMV infection, and in 61 of 162 negative children, detailed TFCD and follow-up was performed, and included in the study constituting a total number of 98 infants. All included children had their first TFCD performed at the age 0–4 months, with follow-up at the age of 5–8 months, and in case of still positive flow in hyperechogenicities, additional follow-up examination was performed at the age of 9–12 months of age. In case of negative LSV flow in the first examination, TFCD follow-up was still performed at the age of 5–8 months in order to verify the lack of flow. In two children from CMV negative group, hyperechogenicities were no longer visible on US at the age of 5–8 months of age and they were classified as negative flow in the follow-up. The remaining number of children (120 of 218) with US markers of LSV were excluded from TFCD study because of insufficient data and lost in follow-up.

Thus, in this study we examined and followed-up Doppler parameters in 98 children with LSV, divided into two groups: congenital CMV positive and congenital CMV negative group. Within each group, first TFCD examination at the age of 0–4 months was further characterized and distributed into three groups depending on localization and presence of flow: unilateral, bilateral and negative flow in LSV. We did not analyze the number of echoic lesions, meaning that children presenting with either minor (one or two spots unilaterally), moderate or major LSV (according to El-Ayoubi et al.) were all included into this study[17]. Subject of this study was not the number of US determined lesions, but distribution and presence of TFCD flow within them unilaterally or bilaterally. We compared TFCD findings, determined Doppler phase of LSV, duration and transition of phase.

The data were presented as the absolute and relative numbers (percentages). χ^2-test was used in the data analysis, while in cases that where the expected frequency in more than 20% of all cells was under 5, Fisher's exact test was used. The data were analysed with the Simple Interactive Statistical Analysis (SISA; available at http://www.quantitativeskills.com/sisa/). The significance was set at $p<0.05$.

Results

We examined and followed-up a total number of 98 children with LSV. One group consisted of 37 infants with congenital CMV infection, and second group consisted of 61 infants negative for congenital CMV infection. All children had clinical signs of neuromotor delay and ultrasound markers of LSV with dotted or vertical hyperechogenicities in thalamus and basal ganglia of the brain (Figure 1a and b). US findings of hyperechogenicities were various: some infants had only spots, some only vertical and some had combined hyperechogenicities localized unilaterally or bilaterally, or in the thalamus and basal ganglia. In this paper we did not analyze the number and appearance of the LSV, but only their existence and localization. TFCD was performed in all included children to visualize the blood vessels in the echogenic area, and real time spectral analysis verified flow in systole and diastole, with the mean velocity and resistance index which was equivalent to lenticulostriate vasculopathy (Figure 2a and b).

In the congenital CMV infection positive group, consisted of 37 infants, TFCD flow in LSV was seen at the age of 0–4 months in 32/37 (86.48%) infants, 8 unilateral (21.62%), 24 bilateral (64.86%), and correlated most probably to lenticulostriate artery vasculopathy, or stage I LSV. In remaining 5/37 infants (13.51%) of the same age period, TFCD flow was absent, suggesting stage II LSV. At the age of 5–8 months, TFCD flow was still visible in 10/37 infants, 3 unilateral (8.11%), 7 bilateral (18.92%), while in most infants 27/37 was negative (72.97%), suggesting stage II LSV, most likely because of obliteration or calcification. After that period, at the age of 9–12 months, TFCD was performed only in 10 infants that had visible flow at the age of 5–8 month, and only 1 in-

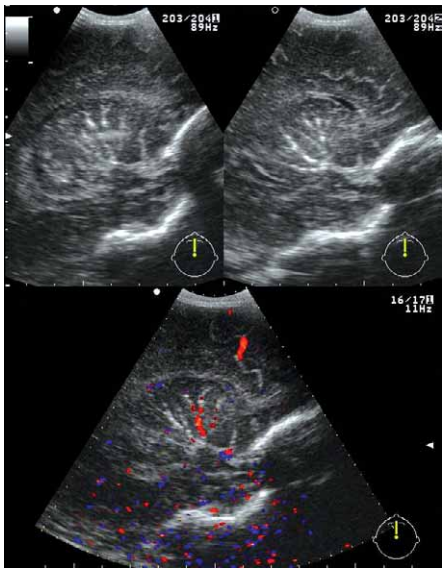

Fig. 1a (above) and 1b (below). Ultrasound markers of LSV with hyperechoic streaks and spots and TFCD visualization of blood vessels in the echogenic area.

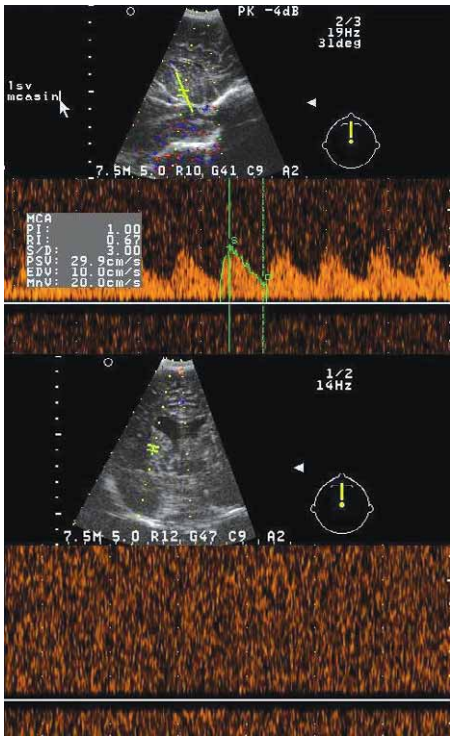

Fig. 2a (above) and 2b (below). TFCD real time spectral analysis showing flow in systole and diastole, with the mean velocity and resistance index. Figure below showing no more visible flow in hyperechoic lesions.

fant still had visible flow, while in all remaining 9/10 infants flow was undetectable (Table 1).

In the congenital CMV infection negative group the same protocol was used. In 49/61 (80.32%) infants, the flow was registered in the first 4 months of life, 10 unilateral (16.39%), 39 bilateral (63.93%), while remaining 12 infants (19.67%) did not have visible flow in the same age period. At the age of 5–8 months, TFCD flow was still visible in 9/61 infants, 3 unilateral (4.92%), 6 bilateral (9.84%), while in most infants 52/61 was negative (85.25%). In 9/61 infants with visible flow, TFCD follow-up was performed at the age of 9–12 months and 8 of them had negative flow, while only one displayed with still visible flow (Table 2). In both groups majority of patients had bilateral TFCD flow, 24/37 in congenital CMV positive group, and 39/61 in congenital CMV negative group (Figure 3).

The analysis of CMV positive and negative samples revealed the lack of significant differences (χ^2=0.61, d.f.=1, p=0.435; Table 1, Table 2). Following, stratified analysis of the 0–4 months age group revealed no significant differences in unilateral (χ^2=0.42, d.f.=1, p=0.517) or bilateral lesions (χ^2=0.01, d.f.=1, p=0.926). There were no differences in the 5–8 months year old children as entire group (χ^2=2.22, d.f.=1, p=0.136), nor in unilateral (Fisher's exact p=0.858) or bilateral lesions (p=0.164). Lastly, we detected no significant difference in 9–12 months old children (Fisher's exact p=0.737; Table 1, Table 2, Figure 3).

Discussion

Our study of 98 patients with LSV, 37 positive for congenital CMV infection and 61 negative, shows that most of the patients from both groups had TFCD visible flow at the age of 0–4 months. Majority of them in both groups, at the age of 5–8 months, had no more visible flow. Smaller part of patients with still visible flow, 10 in congenital CMV infection positive group and 9 in CMV

TABLE 1
CONGENITAL CMV INFECTION POSITIVE GROUP

Congenital CMV positive group Transfontanelar Color Duplex Doppler								
0–4 months old (37 patients)			5–8 months old (37 patients)			9–12 months old (10 patients)*		
Unilateral flow	Bilateral flow	Negative flow	Unilateral flow	Bilateral flow	Negative flow	Unilateral flow	Bilateral flow	Negative flow
8	24	5	3	7	27	1	0	9
21.62%	64.86%	13.51%	8.11%	18.92%	72.97%	10%	0.00%	90%

* patients with still visible flow from the previous age period

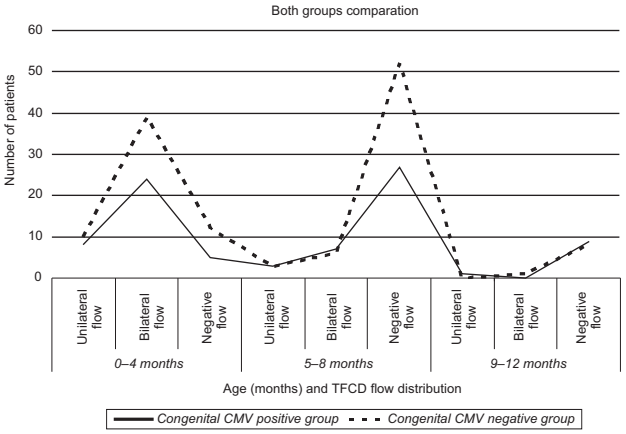

Fig. 3. Showing both group comparison of total number, unilateral, bilateral and negative flow in all patients during infancy. No statistically significant difference was found.

negative group, had their follow-up performed at the age of 9–12 months, and the flow was still visible in only one patient from each group. Based on presence of TFCD visible flow in echogenic streaks and spots, LSV was categorized in two stages: stage I LSV with present flow and stage II LSV without flow. Stage does not reflect the age of the patient, since both negative and positive flow was found in the first 4 months of life, but rather course of pathological changes in the vasculature of thalamus and basal ganglia. Once negative, TFCD flow remained negative throughout following period of age. In none of the patients stage II LSV did not change to stage I LSV, suggesting that when at a certain point stage I LSV became stage II, it remained stable. From this study, we can not conclude with certainty that LSV always has stage I, followed by stage II, because in 17 patients (5 from congenital CMV positive group, and 12 from negative group) had negative flow (stage II LSV) in the youngest age, 0–4 months. But given the progressive changes in LSV in majority of other patients, we can speculate that those 17 patients had stage I LSV earlier in development, prior to the TFCD examination, suggesting possibility of earlier congenital infection.

TFCD verifies the vascular nature of echogenic spots and streaks on the basis of pulsating arterial flow within them. Neuropathological basis for the ultrasound visible LSV and why the gangliothalamic arteries are involved is still unclear. It corresponds to mineralization, deposits of calcium and iron, hypercellular walls of the arteries, perivascular infiltrates and micronodules, as well as basophilic deposits in the walls of arteries[12,18]. Various factors have been reported to be associated with LSV. During many years the highest incidence was reported for mainly TORCH infections, but gradually other conditions were reported having LSV, as well as in healthy infants without any apparent abnormality[6,9,19].

Our result of 25.7% of patients with LSV being positive for congenital CMV infection, is higher than previously reported but we presume that the reasons for that are: selected patients referred to clinic because of perinatal risk factors and/or deviant neuromotor development[1,6,9,14,15,17]. Our population does not represent general population. In our study there were no resources to screen and diagnose other possible causes of LSV in congenital CMV infection negative group, but we agree with Wang et al. proposition of LSV as a marker of diffuse insult to the fetal and neonatal brain[20]. Since brain US and/or TFCD are non-invasive, relatively highly available and non-expensive neuroimaging method if compared to brain CT and MR, they represent a tool of choice for diagnosis of LSV. Previous studies suggested that it is not »cost-effective« to screen for congenital CMV infection in cases of isolated LSV without any other signs of abnormality[1,5,6,17]. We would like to annex that in cases of LSV finding in selected population of infants, with clinical signs of neuromotor impairment and/or perinatal risk factors, it is recommended to screen for CMV.

In our study, TFCD showed no statistically significant difference among congenital CMV infection positive group and negative group, nor in youngest age period (0–4 months), nor in later course of flow in LSV, unilaterally or bilaterally. TFCD negative flow in the youngest age remained negative in the following period, suggesting permanent and stable changes to vascular architecture. Although TFCD did not improve diagnosing of congenital CMV infection, it is important and highly sensitive tool for verifying vascular nature of lesions. LSV staging might provide insight into more precise timing of congenital CMV infection, in case of serological confirmation, but such TFCD use needs to be further investigated in larger and prospective study.

TABLE 2
CONGENITAL CMV NEGATIVE GROUP

Congenital CMV negative group Transfontanelar Color Duplex Doppler								
0–4 months old (61 patient)			5–8 months old (61 patient)			9–12 months old (9 patients)*		
Unilateral flow	Bilateral flow	Negative flow	Unilateral flow	Bilateral flow	Negative flow	Unilateral flow	Bilateral flow	Negative flow
10	39	12	3	6	52	0	1	8
16.39%	63.93%	19.67%	4.92%	9.84%	85.25%	0.00%	11.11%	88.89%

* patients with still visible flow from the previous age period

Conclusion

In the first phase of the LSV, TFCD registered flow in the arteries, which disappeared after 4 months of age in most infants. There was no statistically significant difference in distribution (unilateral or bilateral) between CMV positive and CMV negative group. Also there was no statistically significant difference in presence of TFCD flow during first year of age between CMV positive and CMV negative group of children with LSV. Although the LSV presents an nonspecific marker for intracranial infection (it can be found also in other conditions such as metabolic disorders, chromosomal aberrations and congenital anomalies, and in healthy children), given the fact that 25.7% of children with LSV along with clinical signs of neuromotor impairment and/or perinatal risk factors were positive for congenital CMV infection, all infants presenting with LSV and deviant neurodevelopment should be evaluated for possible intracranial infection.

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LENTIKULOSTRIJATUSNA VASKULOPATIJA – SLIKOVNI MARKER KONATALNE CITOMEGALOVIRUS INFEKCIJE?

SAŽETAK

Lentikulostriatalna vaskulopatija (LSV) je ultrazvučno (UZV) vidljiva lezija mozga koja se prikazuje ehogenim trakama i točkama u arterijama talamusa i bazalnih ganglija. LSV ima raznoliku etiologiju. Transfontanelarni kolor Doppler (TFCD) može dobro prikazati lentikulostriatalne krvne žile i procijeniti: stadij I LSV-a s prisutnim protokom u ehogenostima i stadij II LSV-a kada protoka više nema, unatoč i dalje prisutnim hiperehogenostima koje u to vrijeme najvjerojatnije odgovaraju kalcifikacijama. Ciljevi ovog rada su ustanoviti postoje li razlike u distribuciji (jednostrano ili obostrano) i prisutnosti protoka (tijekom prve godine života) u TFCD nalazu protoka između skupina djece pozitivne i negativne na kongenitalnu CMV infekciju te mogu li UZV i TFCD nalazi biti indikacija za daljnju dijagnostiku moguće kongenitalne CMV infekcije zbog njezinog varijabilnog i često nepovoljnog utjecaja na neurorazvojni ishod. U ovoj studiji smo pratili 98 dojenčadi s LSV-om. Jedna grupa (37/98) s kongenitalnom CMV infekcijom, a druga grupa (61/98) negativna. Svi ispitanici su imali kliničke znakove neuromotornog zaostajanja te UZV i TFCD znakove LSV-a. Naša studija je pokazala da je većina djece u obje grupe imala vidljiv protok na TFCD-u u dobi do 4 mjeseca. U većine iz obje grupe, u dobi 5–8 mjeseci, više nije bilo vidljivog protoka. TCFD nije pokazao nikakve statističke razlike između dvije skupine, niti u najranijem periodu, niti u kasnijem tijeku LSV-a, unilateralno ili bilateralno. Iako LSV predstavlja nespecifičan marker za intrakranijsku infekciju uzevši u obzir da je 25.7% djece s LSV-om te neurorazvojnim odstupanjem, pozitivno na kongenitalnu CMV infekciju, svi s nalazom LSV-a uz perinatalne rizične faktore bi trebali procjenu radi moguće kongenitalne CMV infekcije.