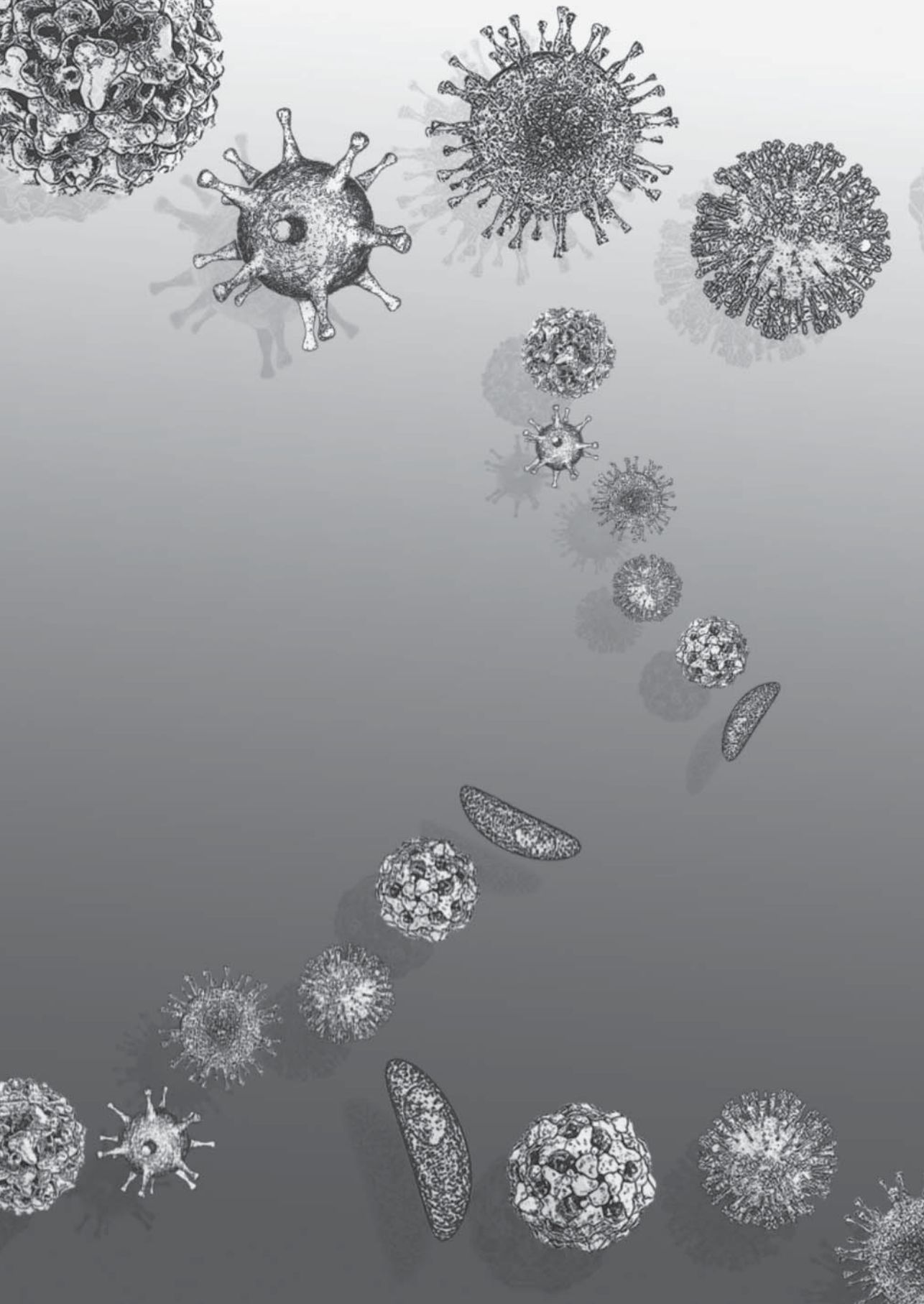
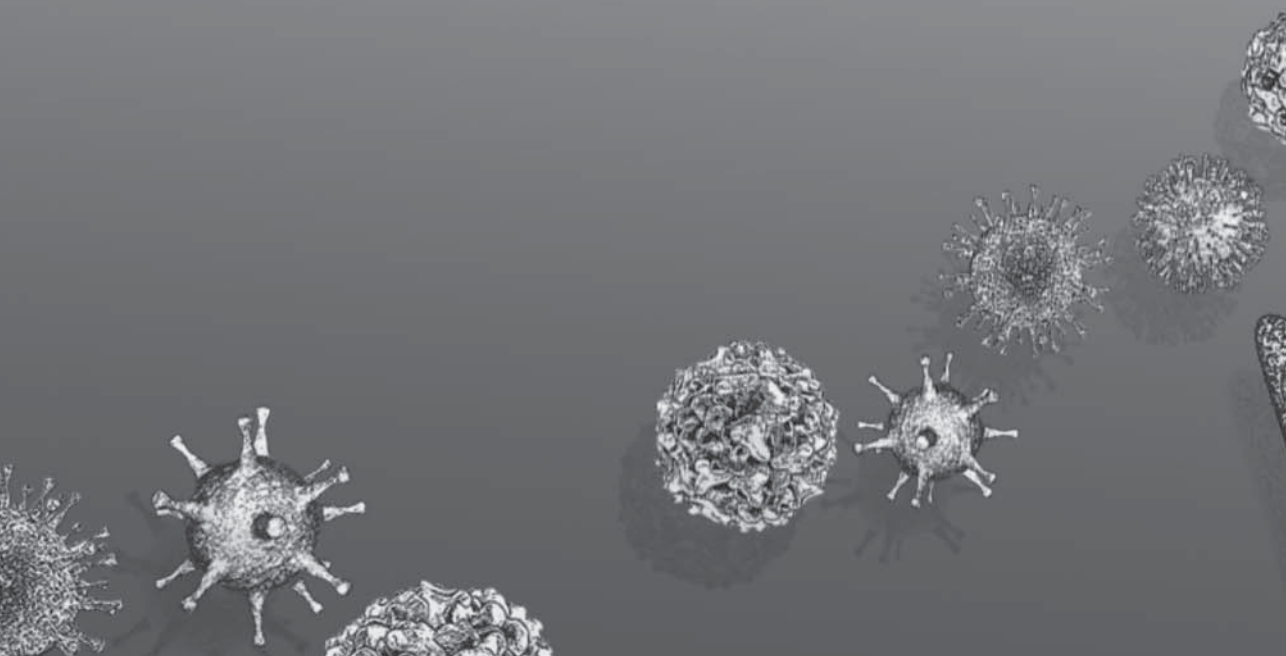


PART A

ToRCH



2

IS ROUTINE TORCH SCREENING WARRANTED IN NEONATES WITH LENTICULOSTRIATE VASCULOPATHY?

Eveline P. de Jong, Enrico Lopriore, Ann C.T.M. Vossen,
Sylke J. Steggerda, Arjan B. Te Pas, Aloys C.M. Kroes, Frans J. Walther

Neonatology 2010;97:274-8

ABSTRACT

Background: Congenital infections are associated with a wide spectrum of clinical symptoms, including lenticulostriate vasculopathy (LSV).

Objective: To determine the relationship between LSV and congenital infections, as diagnosed by ToRCH serology and viral culture for cytomegalovirus (CMV).

Methods: All neonates with LSV admitted to our neonatal intensive-care unit from 2004 to 2008 were included in the study. Results of maternal and neonatal ToRCH testing were evaluated.

Results: During the study period, cranial ultrasound scans were performed in 2,088 neonates. LSV was detected in 80 (4%) neonates. Maternal and/or neonatal serological ToRCH tests were performed in 73% (58/80) of cases. None of the mothers or infants (0 of 58) had positive IgM titres for *Toxoplasma*, rubella, CMV or herpes simplex virus. Additional urine culture for CMV was performed in 38 neonates. None of the infants (0 of 38) had a positive CMV urine culture test.

Conclusions: Routinely applied efforts to diagnose congenital infections in cases presenting with LSV cases should only be regarded as mandatory once well-designed studies demonstrate a clear diagnostic benefit.

INTRODUCTION

Lenticulostriate vasculopathy (LSV) is an echodensity of the lenticulostriate branches of the middle cerebral arteries in the region of the basal ganglia and/or thalamus. It is thought to be a nonspecific marker of a previous insult to the developing brain [1]. LSV occurs in approximately 5% of neonates [1-3], and has been associated with a wide variety of diseases including chromosomal disorders, perinatal asphyxia, non-immune fetal hydrops, twin-twin transfusion syndrome, congenital heart disease and metabolic disorders [4-6]. The clinical significance on long-term neurodevelopmental outcome is not clear.

Some authors also suggest a clinical co-occurence of congenital infections and LSV and advise routine ToRCH screening in all infants with LSV [7-9]. ToRCH is an acronym which groups several micro-organisms including toxoplasmosis, rubella, cytomegalovirus (CMV) and herpes simplex virus (HSV). Although each organism may cause distinct clinical features, ToRCH testing is often requested as a single serologic diagnostic test. The variability of clinical features caused by these congenital infections is extensive and includes intrauterine growth restriction, haematological abnormalities and several cerebral abnormalities such as LSV [1 3 5 6 10]. However, the co-occurence of congenital infections and LSV is merely speculative and based on few casuistic reports or small case series, most of which lack a control group [2-4 6-12].

To date, there is no consensus regarding the relevance of efforts to diagnose congenital infections in newborns with LSV detected on cerebral ultrasound scans. The aim of our study was to evaluate the prevalence of congenital infections in a large series of neonates with LSV detected on routine cerebral ultrasound examinations and determine the role of ToRCH testing in neonates with LSV.

METHODS

All consecutive cases of newborns with LSV admitted to our neonatal intensive care unit between January 2004 and January 2009 were included in the study. The Leiden University Medical Center is a tertiary medical centre in The Netherlands. The presence of LSV was determined by routine cranial ultrasound scans, performed by a neonatologist. Cranial ultrasound scans were performed with an Aloka 5000 scanner (Biomedic Nederland B.V., Almere, The Netherlands) with a multifrequency transducer (frequency set at 7.5 MHz). Each examination included coronal and bilateral parasagittal views of the brain. LSV was defined as bright hyperechogenic lesions in the thalamus and basal ganglia, either in branching, linear pattern or punctate shaped pattern (Figure 2.1).

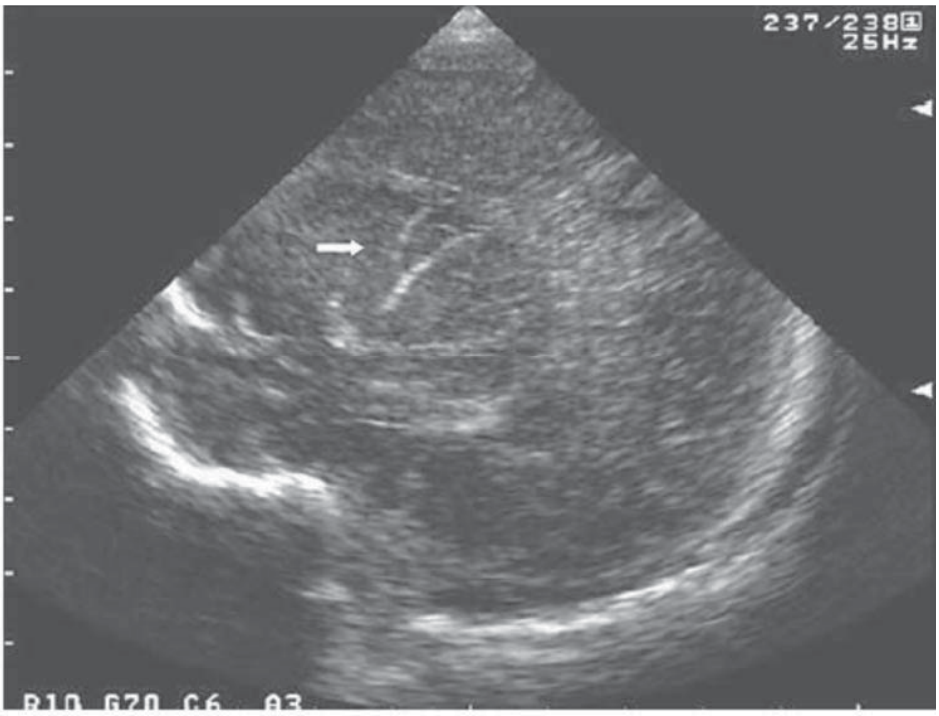


Figure 2.1: Cranial ultrasound (sagittal view) in a neonate with lenticulostriate vasculopathy, showing the typical branching hyperechogenic lesions in the thalamus and basal ganglia (arrow).

We reviewed the neonatal and maternal medical charts in all neonates with LSV to determine if ToRCH serologic testing was performed in the perinatal period. Whether ToRCH serologic tests and urine CMV culture was performed in infants with LSV was left to the judgement of the attending physician. We compared the serologic results of our study group with data on the prevalence of ToRCH infections in the general population in The Netherlands. IgM *Toxoplasma*, IgM Rubella (both μ-capture) and IgM CMV (indirect EIA) were tested using Vidas enzyme-linked fluorescent assays (bioMérieux). IgM HSV was tested using the Merifluor IFA (Meridian Bioscience). As from July 2007 IgM HSV testing was performed using the indirect EIA from Virion\Serion. CMV urine culture was performed using MRC-5 shell-vials. After 18–24 hours incubation at 37°C, cells were stained by an indirect immunofluorescence assay with a monoclonal antibody against p72 CMV antigen (clone 13, Argene Biosoft, France).

We recorded the following neonatal data: gestational age at birth, birth weight, sex, small for gestational age, twin-to-twin transfusion syndrome, respiratory distress syndrome, congenital heart disease, perinatal asphyxia, polycythemia-hyperviscosity syndrome, metabolic disorder and rhesus haemolytic disease.

RESULTS

During the study period, 2545 infants were admitted to our neonatal intensive care unit. Cranial ultrasound scans were performed in 2088 (82%) infants. LSV was detected in 80 (4%) newborns. Seventy-five (94%) of these newborns had linear branched lesions and 5 (6%) had punctate-shaped lesions. Patient's characteristics of the study group are listed in Table 2.1.

Table 2.1: Patient characteristics of 80 neonates with LSV (n = 80)

Characteristic	
Birth weight (± SD), (g)	2224 (± 926)
Gestational age (± SD), (weeks)	34 (± 4)
Male infants, n (%)	45 (56%)
Respiratory distress syndrome, n (%)	18 (22%)
Twin-to-twin transfusion syndrome, n (%)	14 (18%)
Congenital heart disease, n (%)	10 (13%)
Perinatal asphyxia, n (%)	9 (11%)
Small for gestational age, n (%)	7 (9%)
Polycythaemia-hyperviscosity syndrome, n (%)	3 (4%)
Rhesus haemolytic disease, n (%)	3 (4%)
Metabolic disorder, n (%)	2 (3%)

Overall, serologic ToRCH tests were performed in 73% (58/80) of cases. Serologic tests were performed in 55% (32/58) of cases in neonatal blood and in 47% (27/58) of cases in maternal blood. In one case ToRCH tests were performed in both neonatal and maternal blood. None of the infants or mothers had positive IgM titers for *Toxoplasma*, rubella, CMV or HSV (0 of 58). Urine culture for CMV was performed in 38 cases. No cases with positive CMV urine culture were found. In total, in 61 (76%) neonates with LSV either ToRCH serologic tests or urine culture for CMV was performed. All tests (either serologic tests or urine culture) were negative. The derivation of the initial population and the tested population is shown in an algorithm in Figure 2.2.

DISCUSSION

In this study, we found no evidence of co-occurence of congenital ToRCH infections in neonates with LSV. In contrast to previous reports from small series of infants with LSV tested for ToRCH infections, none of the infants evaluated in this study tested positive.

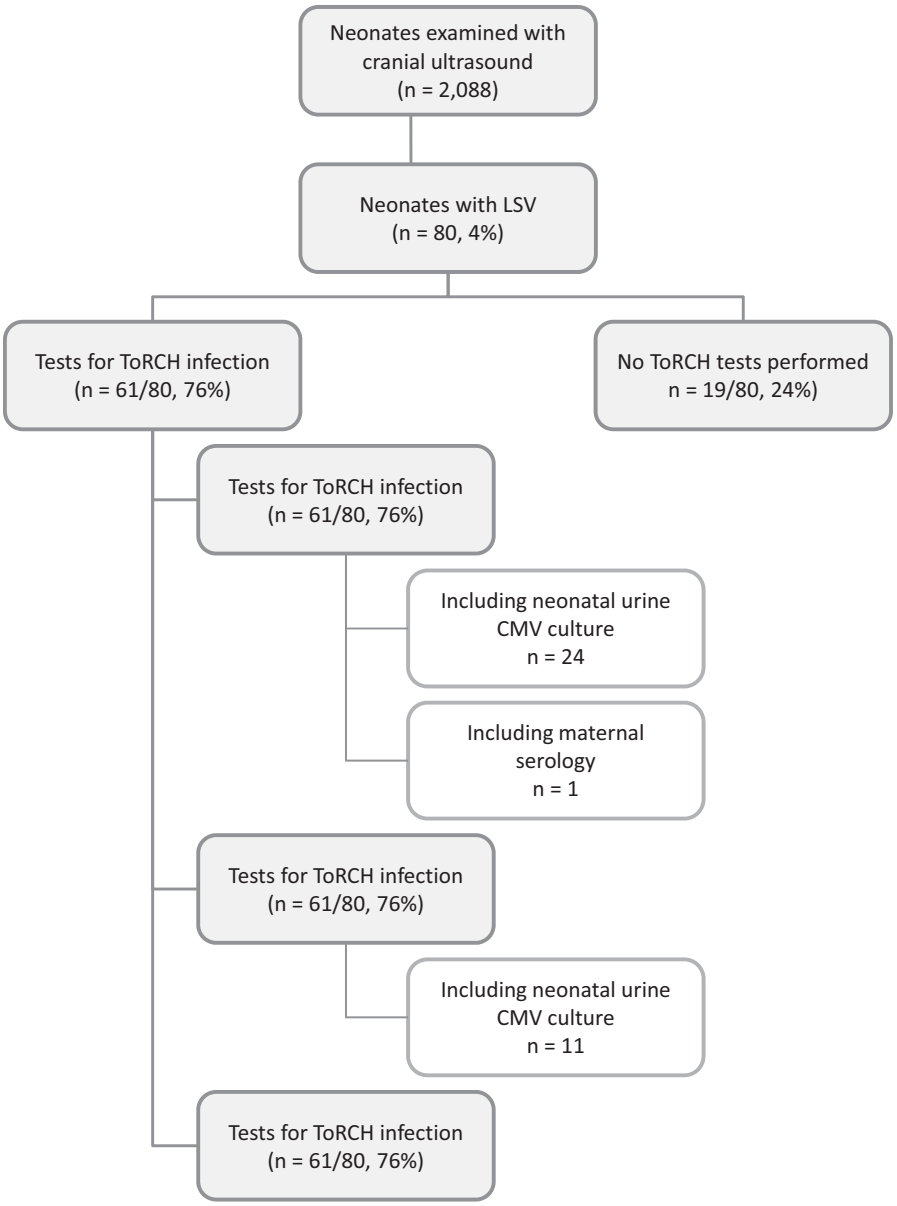


Figure 2.2: Flowchart showing the derivation of our study population.

This is to date the largest study investigating the possible clinical co-occurence between congenital infections and LSV. The results of this study can be used to determine the optimal management, in terms of diagnostic investigations, in neonates with LSV. Recommendations for the appropriate diagnostic evaluation are warranted since LSV is a relatively common

ultrasound finding in neonates. The prevalence of LSV in this study was 4% which is in accordance with other reports [1-3].

The pathogenesis of LSV is not clear and is thought to be a nonspecific marker of a previous insult to the developing brain [1]. Histopathological examination showed basophilic depositions in the perivascular space in two studies [8 11], another study could not reproduce this finding but did find a thickened and hypercellular arterial wall in a neonate diagnosed with LSV [2]. The aetiology of LSV has been associated with a wide variety of diseases including chromosomal disorders, perinatal asphyxia, respiratory distress syndrome, non-immune fetal hydrops, twin-twin transfusion syndrome, rhesus haemolytic disease, polycythemia and congenital infections [4-6].

However, the evidence for a (causal?) relationship between congenital infections and LSV is limited. Whether routine ToRCH serologic screening in neonates with LSV is warranted (and cost-effective) is controversial [6]. Ideally, routine ToRCH tests should only be performed provided the prevalence of congenital infections in neonates with LSV is higher than in the general population or early detection of congenital infection leads to improved outcome. Both issues have not yet been clarified.

The prevalence of congenital infections in general population varies per geographic region and appears to be low in Northern European countries. The prevalence of congenital CMV, toxoplasmosis and HSV is reported to be approximately 0.9% [13], 0.2% [14], and 0.003% [15], respectively and the incidence of congenital rubella is also estimated to be very low due to immunity by vaccination [16].

Conflicting results have been reported regarding the prevalence of congenital infections in newborns with LSV ranging from 1% [6] to as high as 58% [8]. Unfortunately, most studies reporting on the co-occurence of congenital infections and LSV were small, uncontrolled case series, limiting their interpretation. A summary of studies in neonates with LSV in whom ToRCH screening was performed, is presented in Table 2.2. All studies were retrospective studies, except two prospective studies from Cabanas et al. [11] and Makhoul et al. [3]. Older studies describe a high incidence of congenital infections, whereas the more recent studies seem to report a lower incidence. Analysis of the data of Table 2.2 shows that the overall incidence of congenital infections in all neonates with LSV is 7% (32/442). The majority of these infected babies (78%, 25/32) has congenital CMV infection. However, care should be taken when interpreting these results due to major methodological limitations of most of these studies, including the retrospective study design, the small number of included patients and the important risk of selection and publication bias. Existence of bias in favour of publication of positive results is well documented in the literature and often leads to inflated associations [17].

Table 2.2: Summary of studies on the association between congenital ToRCH infection and LSV

Authors	Neonates with LSV, n (%)	ToRCH positive, n (%)	Comments
Teele et al. [8], 1988	12	7 (58%)	CMV (n = 5), Rubella (n = 2)
Hughes et al. [9], 1991	25	4 (16%)	CMV (n = 4)
Weber et al. [4], 1992	15	2 (13%)	CMV (n = 2)
Cabanas et al. [11], 1994	37	3 (8%)	CMV (n = 1), Rubella (n = 1), Toxoplasmosis (n = 1)
Wang et al. [1], 1995	34	4 (12%)	CMV (n = 3), Rubella (n = 1)
Shefer-Kaufman et al. [10], 1999	75	1 (1%)	CMV (n = 1)
Chamnanvanakij et al. [12], 2000	10	4 (40%)	CMV (n = 4)
Coley et al. [2], 2000	63	5 (8%)	CMV (n = 4), Toxoplasmosis (n = 1)
Makhoul et al. [3], 2003	21	1 (5%)	CMV (n = 1)
El Ayoubi et al. [6], 2003	70	1 (1%)	Toxoplasmosis (n = 1)
This study, 2009	80	0 (0%)	

The data in our study should also be interpreted with care due to several methodological limitations, including the retrospective nature of the study and the absence of a control group. Moreover, although this is the largest cohort of infants with LSV tested for congenital infections, the size of our studied population remains relatively small.

In conclusion, the yield of workup for ToRCH infection among infants with LSV in our study is poor and does not justify the incurred costs. Recent studies on the indication and value of ToRCH testing for other fetal and neonatal indications suggest that ToRCH testing is often not necessary and can be limited to screening for CMV, using urine culture [18 19]. In analogy, we suggest that complete routine ToRCH screening in neonates with LSV is not warranted and should, at the most, be limited to CMV urine culture. Routine screening for congenital infections should only be regarded as mandatory once large and well-designed studies (including a control group) demonstrate an increased risk, which is to be considered unlikely up till now. To shed more light on the role of ToRCH infections in neonates with LSV, a large study with full serologic tests in all LSV cases should be performed.

REFERENCES

1. Wang HS, Kuo MF, Chang TC. Sonographic lenticulostriate vasculopathy in infants: some associations and a hypothesis. AJNR Am J Neuroradiol 1995;16(1):97-102.
2. Coley BD, Rusin JA, Boue DR. Importance of hypoxic/ischemic conditions in the development of cerebral lenticulostriate vasculopathy. Pediatr Radiol 2000;30(12):846-55. doi: 10.1007/s002470000322
3. Makhoul IR, Eisenstein I, Sujov P, et al. Neonatal lenticulostriate vasculopathy: further characterisation. Arch Dis Child Fetal Neonatal Ed 2003;88(5):F410-4.
4. Weber K, Riebel T, Nasir R. Hyperechoic lesions in the basal ganglia: an incidental sonographic finding in neonates and infants. Pediatr Radiol 1992;22(3):182-6.
5. Te Pas AB, van Wezel-Meijler G, Bokenkamp-Gramann R, et al. Preoperative cranial ultrasound findings in infants with major congenital heart disease. Acta Paediatr 2005;94(11):1597-603. doi: 10.1080/08035250510041150
6. El Ayoubi M, de Bethmann O, Monset-Couchard M. Lenticulostriate echogenic vessels: clinical and sonographic study of 70 neonatal cases. Pediatr Radiol 2003;33(10):697-703. doi: 10.1007/s00247-003-0948-z [published Online First: 2003/08/09]
7. Grant EG, Williams AL, Schellinger D, et al. Intracranial calcification in the infant and neonate: evaluation by sonography and CT. Radiology 1985;157(1):63-8. doi: 10.1148/radiology.157.1.2994172
8. Teele RL, Hernanz-Schulman M, Sotrel A. Echogenic vasculature in the basal ganglia of neonates: a sonographic sign of vasculopathy. Radiology 1988;169(2):423-7. doi: 10.1148/radiology. 169.2.2845473
9. Hughes P, Weinberger E, Shaw DW. Linear areas of echogenicity in the thalami and basal ganglia of neonates: an expanded association. Work in progress. Radiology 1991;179(1):103-5. doi: 10.1148/radiology.179.1.1848713
10. Shefer-Kaufman N, Mimouni FB, Stavorovsky Z, et al. Incidence and clinical significance of echogenic vasculature in the basal ganglia of newborns. Am J Perinatol 1999;16(6):315-9. doi: 10.1055/s-2007-993878 [published Online First: 1999/12/10]
11. Cabanas F, Pellicer A, Morales C, et al. New pattern of hyperechogenicity in thalamus and basal ganglia studied by color Doppler flow imaging. Pediatr Neurol 1994;10(2):109-16.
12. Chamnanvanakij S, Rogers CG, Luppino C, et al. Linear hyperechogenicity within the basal ganglia and thalamus of preterm infants. Pediatr Neurol 2000;23(2):129-33. doi: S0887-8994(00)00146-6 [pii] [published Online First: 2000/10/06]
13. Gaytant MA, Galama JMD, Semmekrot BA, et al. The incidence of congenital cytomegalovirus infections in The Netherlands. Journal of Medical Virology 2005;76(1):71-75. doi: 10.1002/jmv.20325
14. Jenum PA, Stray-Pedersen B, Melby KK, et al. Incidence of Toxoplasma gondii infection in 35,940 pregnant women in Norway and pregnancy outcome for infected women. J Clin Microbiol 1998;36(10):2900-6.
15. Poeran J, Wildschut H, Gaytant M, et al. The incidence of neonatal herpes in The Netherlands. J Clin Virol 2008;42(4):321-5. doi: S1386-6532(08)00063-2 [pii] 10.1016/j.jcv.2008.02.004 [published Online First: 2008/03/25]
16. de Melker HE, van den Hof S, Berbers GA, et al. Evaluation of the national immunisation programme in the Netherlands: immunity to diphtheria, tetanus, poliomyelitis, measles, mumps, rubella and Haemophilus influenzae type b. Vaccine 2003;21(7-8):716-20.
17. Sica GT. Bias in research studies. Radiology 2006;238(3):780-9. doi: 10.1148/radiol.2383041109
18. Abdel-Fattah SA, Bhat A, Illanes S, et al. TORCH test for fetal medicine indications: only CMV is necessary in the United Kingdom. Prenatal Diagnosis 2005;25(11):1028-31. doi: 10.1002/pd.1242

19. Khan NA, Kazzi SN. Yield and costs of screening growth-retarded infants for torch infections. Am J Perinatol 2000;17(3):131-5. doi: 10.1055/s-2000-9288 [published Online First: 2000/09/30]