9

SUMMARY

The aim of the first part of this thesis (part A) was to investigate the yield of performing diagnostic tests for 'ToRCH' infections in newborn infants with lenticulostriate vasculopathy (LSV) or small for gestational age (SGA). In the second part of this thesis (part B) the epidemiology and follow-up of Entero- (EV) and Human Parechovirus (HPeV) induced sepsis-like illness in neonates and young infants was studied. This thesis updates and nuances the indications for testing for both groups of pathogens and provides insight in the follow-up after a proven infection with EV or HPeV. ***Chapter 1*** provides the general introduction of this thesis in which the clinical background is explained. Congenital 'ToRCH' infections have a low incidence in The Netherlands but diagnostic testing occurs frequently for a variety of different indications, some of which aren't necessary. On the contrary, EV- and HPeV infections have a high incidence infants, but are frequently missed due to lack of testing. Furthermore, knowledge about follow-up after a proven infection with EV or HPeV is scarce.

PART A: TORCH

The first part of this thesis explores two indications for ToRCH testing in newborn infants e.g. LSV and SGA.

Chapter 2 investigates the association between congenital ToRCH infections and the appearance of LSV on cerebral ultrasound in the neonatal population. Combining the data of our study population with data from all previously literature on this subject, the overall incidence of congenital infections in neonates with LSV is 7% (32/442), of whom the majority has congenital CMV infection (25/32, 78%). We conclude that in cases with isolated LSV, routine screening for all infections included in the ToRCH acronym yields a poor result and does not justify the incurred costs. It should be limited to urinary screening for CMV only.

Chapter 3 shows that in neonates with isolated, unexplained SGA the co-occurrence of congenital ToRCH is extremely low. Congenital CMV was diagnosed in 2/112 (2%) of our study population. No evidence of the co-occurrence of SGA and any of the other pathogens of the ToRCH acronym was found. We conclude that testing neonates with unexplained, isolated SGA should be limited to urinary screening for CMV.

Chapter 4 provides a broader view on the diagnostic tests that can be performed in a 'ToRCH-screening'. Infection with one of the 'ToRCH' micro-organisms has been a diagnostic consideration in a variety of minor systemic and cerebral abnormalities, such as calcifications or pseudocysts. We describe the differences in clinical manifestations of the different ToRCH pathogens and we remind clinicians that testing for these pathogens is not one

single serum test. Testing can consist of repeated serology, but in some cases PCR is more sensitive and specific. Local epidemiology, first-trimester maternal antibody status (subject of local obstetric policy) and clinical signs and symptoms of the mother and neonate must be taken into account before deciding which laboratory test is useful to request.

PART B: ENTEROVIRUS AND HUMAN PARECHOVIRUS

The second part of this thesis investigates EV and HPeV induced sepsis-like illness in young infants.

In ***chapter 5*** we describe the epidemiology and clinical manifestations of EV and HPeV as a causative agent for sepsis-like illness in infants under 90 days of age who did not need intensive care treatment. We found that EV and HPeV infection have an even larger incidence that previously described in laboratory based or retrospective studies. Combined they are the causative pathogen in about 50% of cases. The seasonal epidemiology of EV an HPeV are quite specific. EV has a yearly peak incidence during summer and HPeV has a biannual summertime peak in Europe and the USA. But both are never completely absent in non-epidemic periods. It is important for the clinician to remain aware that no clinically significant differences exist, between infants with EV or HPeV and those with a serious bacterial infection. Incorporation of EV and HPeV PCR testing in serum and CSF into standard of care in all infants undergoing a sepsis work-up is paramount.

Chapter 6 investigates cerebral imaging and neurodevelopmental outcome of young infants after admission to a medium care unit with EV or HPeV induced sepsis-like illness. We investigated the presence of neurologic signs and symptoms in a small prospective cohort of infants that had EV or HPeV induced sepsis-like illness up to one year of age. No abnormalities on cerebral imaging were detected and no difference in neurodevelopment compared to healthy Dutch children of the same age was found. Firm conclusions are not yet possible due to the small study cohort and short duration of follow-up.

In ***chapter 7*** no myocardial involvement in young infants with EV or HPeV induced sepsis-like illness was found. None of the studied infants developed clinical signs of acute myocarditis. There were no clinically relevant differences between cardiac markers, ECG and echocardiographic findings in both EV/HPeV positive and EV/HPeV negative infants. We advise against screening in all infants with EV or HPeV sepsis-like illness for myocardial involvement because of the low yield and absence of clinical consequences in infants that do not need intensive care treatment. Clinical vigilance for signs of myocardial involvement in infants with EV or HPeV induced sepsis-like illness remains warranted.

Chapter 8, the general discussion, puts the conclusions of this thesis in its broader scientific perspective and provides suggestions for implementation and future research.