Seminars in Pediatric Neurology

Viral Infections and the Neonatal Brain

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This review includes the congenital infections best known by the acronym TORCH (*Toxoplasma gondii*, rubella virus, cytomegalovirus, and herpes virus), as well as Zika virus infection and perinatally acquired infections (enterovirus, parechovirus, rotavirus, parvovirus). Congenital infections are due to pathogens that can cross the placenta and are more likely to injure the brain when the infection occurs early in pregnancy. There are many similarities, with regards to brain lesions, for congenital Zika syndrome and congenital cytomegalovirus infection. Perinatally acquired viral infections tend to injure the white matter, with cystic evolution being more likely in the (late) preterm infant compared to the full-term infant. Congenital and perinatally acquired viral infections can be associated with adverse neurological outcomes. Prevention is important, especially as therapeutic options are limited. In this review both congenital as well as perinatally acquired viral infections will be discussed with a focus on neuro-imaging findings.
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Introduction

Although far less common than bacterial infections, congenital and perinatally acquired viral infections do occur and may lead to major disabilities in infancy and childhood.[1] The term TORCH, an acronym including *Toxoplasma gondii*, rubella virus, cytomegalovirus (CMV), and herpes viruses, all potential causes of congenital infection, was coined in the 1970's and other acronyms such as "Cheap TORCHES" have been introduced to include perinatally acquired infections.[2] Volpe prefers the term SCRATCHEZ which includes syphilis (S) acquired immunodeficiency syndrome (A), chickenpox (C), enterovirus (E), and Zikavirus (Z). While congenital rubella virus syndrome is no longer seen in countries with compulsory immunization against this virus, an outbreak of Zika virus (ZIKV) recently occurred in Brazil resulting in the ZIKV syndrome, with brain lesions comparable to, but more severe than congenital CMV infection.[3,4] While these infections occur in utero, other viral infections occur within days to weeks after the birth of the infant and are referred to as perinatal infections. Some of these perinatally acquired infections (parechovirus, enterovirus (EV), rotavirus, and others) may result in injury to especially the white matter. While the incidence of bacterial infections of the central nervous system (CNS) was reported to be 0.21/1000 live births in a national cohort, the incidence of viral CNS infections was said to be 0.05/1000, with identification of the virus in about 50%.[5,6] With the development of *polymerase chain reaction* (PCR) for instance for EV and parechovirus an increase in laboratory-confirmed, viral meningoencephalitis has been reported.[7,8]

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Congenital Viral Infections

Cytomegalovirus

CMV, a DNA virus and member of the herpesvirus family, infects people of all ages worldwide, usually without recognizable symptoms.[9] CMV infection is one of the most common and serious congenital infections. This congenital infection has a higher prevalence in developing countries and among individuals of lower socioeconomic status in developed nations. The incidence varies between 0.3% and 0.7%.[10] Between 40%-90% of individuals have experienced a CMV infection by late adulthood, with the highest rate in individuals from a low socio-economic background. A substantial percentage of women of reproductive age are however still CMV seronegative and therefore at risk of primary CMV infection during pregnancy.[11] The risk of an infection is especially high during a second pregnancy, with the first child becoming infected in the nursery. Information about hygiene is therefore essential, but many pregnant women

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have never been told about CMV infection and have not been informed about possible measures that may help to reduce the risk of becoming infected during pregnancy. In a mixed interventional and observational controlled study, a decreased seroconversion rate was shown when hygiene information was given to pregnant women at risk for primary CMV infection.[12] Recent data suggest that maternal immunity prior to pregnancy cannot be viewed as protective. Britt et al. have shown that a nonprimary infection, due to reactivation of an endogenous strain or reinfection with a new CMV strain in women with preconceptional immunity can lead to congenital CMV infection.[13] Almost 12,000 saliva samples were obtained after birth in a prospective study, with 0.37% showing evidence for a congenital CMV infection, 52% following a primary, and 48% following a nonprimary infection, with 21% and 19% respectively being symptomatic.[14] However, a higher incidence of abnormal brain sonographic findings was reported following primary versus nonprimary maternal CMV infection (76.8% vs 8.3%, $P < 0.001$).[15]

Approximately 30%-40% of infants whose mothers experience primary infection during pregnancy develop a congenital infection. The percentage of infected children with CMV-specific symptoms at birth has been reported to be between 10% and 15%. The percentage of symptomatic children who subsequently develop permanent sequelae is 40%-60%. The percentage of children without symptoms at birth who develop permanent sequelae was estimated to be 10%-15%, most often progressive sensorineural hearing loss.[16] The risk for progressive hearing loss is the same following primary and nonprimary infection.[17]

Postnatally acquired CMV (pCMV) infection can occur in extremely preterm infants. CMV reactivation with shedding of the virus, or the presence of CMV DNA in breast milk within several days after delivery is seen in more than 90% of CMV seropositive women. In a meta-analysis, among 299 infants fed untreated breast milk, 19% (11%-32%) acquired pCMV infection and 4% (2%-7%) developed pCMV-sepsis like syndrome.[18] Development of germinolytic cysts (GLC) and lenticulostriate vasculopathy (LSV) is noted to develop several weeks after birth in these infants. The studies reported on long-term outcome are limited but a recent study with 5-year outcome did not find a difference in outcome between affected and nonaffected infants.[19] Others did show poorer overall cognitive abilities in a small group of 42 children with pCMV compared with preterm infants without this infection when studied at a mean age of 13.9 years of age.[20]

Clinical Symptoms

Approximately one third of affected infants have a gestational age of 37 weeks or less and infants are often small for gestational age. Microcephaly is seen in approximately 50% of all symptomatic patients. Approximately 10% of symptomatic infants develop clinical seizures in the neonatal period. Hepatosplenomegaly and a petechial rash, usually related to thrombocytopenia, are frequently encountered.

Diagnosis

Pregnancy

The presence of anti-CMV IgM antibodies is considered to be a good indicator of an acute or recent CMV infection, but IgM antibodies are only present in 70% of infected babies and in only fewer than 10% of IgM−positive women is the fetus infected.[21] When the infection takes place very early in the pregnancy or even preconception, IgM may have become negative by the time the suspicion of congenital CMV infection is raised.[22] The anti-CMV IgG avidity test is the most reliable procedure to identify primary infection in pregnant women.[23,24] Low avidity indices indicate low avidity IgG antibodies in serum caused by acute or recent primary CMV infection, whereas high avidity indices (high avidity serum IgG) indicate no current or recent primary infection. A reliable prenatal diagnosis is obtained by performing a PCR on the amniotic fluid. The best period to perform an amniocentesis is between the 21st and 22nd weeks of gestation. Around 6-9 weeks are required after maternal infection for the virus to be eliminated in the fetal urine in amounts sufficient to be detected in the amniotic fluid, as CMV is a slowly replicating virus. When the amniocentesis is carried out earlier when little virus is shed by the fetal kidney, there is a risk of a false negative test. The sensitivity and specificity (90%-98% and 92%-98%, respectively) for PCR analysis in the amniotic fluid are high with respect to viral transmission from mother to fetus.[25]

After Birth

Viral isolation in the urine and/or saliva within the first 2-3 weeks after birth is still considered the gold standard for the diagnosis of congenital CMV infection in the newborn. Screening saliva for CMV-DNA by PCR is reliable in the full-term infant but inferior to urine to diagnose postnatal CMV infections in preterm infants, most likely to their lower viral load.[26] Contamination with CMV-infected maternal breast milk may result in false-positive CMV-PCR results.[27]

Imaging Findings

The diagnosis is increasingly being made using fetal ultrasound and MRI. The 2 techniques are complimentary with GLC and LSV best recognized with (transvaginal) ultrasound and migrational disorders with MRI. Several reviews with many illustrations have been published and a classification system for prenatal MRI was proposed by Cannie et al[28] (Table 1).

Following birth, cranial ultrasound is once again the first method of choice and the diagnosis is often suggested by GLC, LSV, temporal lobe, and occipital cysts.[29,30] (Fig. 1) MRI rather than computed tomography is recommended as the second imaging method to assess additional findings, such as cerebellar hypoplasia and migrational disorders such as polymicrogyria (PMG) which will be missed when neuroimaging is restricted to cranial ultrasound.[22,31] When PMG is diagnosed, following an infection during the first or early part of the second trimester, the outcome is more likely to be

Table 1 Fetal and Neonatal Neuroimaging Scoring Systems for Congenital CMV Infection

	Cannie et al. – Fetal MRI[28]	Alarcon et al. Postnatal cranial ultrasound (cUS) and MRI[32]
Grade 1	Normal findings	None of the findings below
Grade 2	Isolated frontal or parieto-occipital periventricular increased signal intensity on T2 weighted sequence	cUS: Single punctate periventricular calcification, lenticulostriate vasculopathy, caudothalamic germinolysis, ventriculomegaly (excluding severe) and/or MRI: focal/multifocal increased signal intensity on T2 weighted sequence
Grade 3	Isolated temporal periventricular increased signal intensity on T2 weighted sequence	cUS: Multiple discrete periventricular calcifications, paraventricular germinolytic cysts, severe ventriculomegaly, MRI: diffuse white matter signal abnormality and/or temporal lobe involvement
Grade 4	Cysts and/or septa in the temporal and/or occipital lobe	cUS: extensive calcification, brain atrophy MRI: abnormal gyration, cortical malformation, dysgenesis of the corpus callosum and/or cerebellar hypoplasia
Grade 5	Migrational disorders, cerebellar hypoplasia	

Adjusted from references 27 and 31.

unfavorable, as has been suggested using the classification for postnatal neuroimaging in congenital CMV infection by Alarcon et al.[32] It is uncommon for the mother to remember having been ill and there is a history of a flu-like episode in only about 5%. Barkovich and Lindan suggested that neuroimaging is helpful to time the onset of the infection, with lissencephaly due to an infection prior to 16-18 weeks and PMG suggestive of an infection around 18-24 weeks' gestation.[33] Even though fetal MRI can be normal, subtle abnormal cranial ultrasound findings were found in a study by Amir et al in 46 out of 98 (50%), and these abnormalities were mostly LSV (44/46).[34] Sensorineural hearing loss was present in 16 of the 98 infants studied with ultrasound abnormalities in 10 of these 16 infants.

Prevention and Treatment

There is no agreement in the literature about routine screening for CMV, but in most countries this is not recommended.[35] Informing pregnant women about how CMV infection can be acquired is important.[36] Treatment with CMV hyperimmune immunoglobulin in women who seroconverted during pregnancy is not recommended.[37] The development of a vaccine is still under investigation.[38]

Six-month therapy with valganciclovir is now recommended in newborn infants with confirmed congenital CMV infection with CNS abnormalities. When comparing a 6-week course with 6-month therapy, with "best-ear" hearing being the primary endpoint, there was no difference for best-ear hearing at 6 months. Total-ear hearing (hearing in 1 or both ears that could be evaluated) was more likely to be improved or to remain normal at 12 months in the 6-month treatment group compared with the 6-week treatment group (73% vs 57%, $P = 0.01$).[39,40] Neurodevelopmental scores on the Bayley Scales of Infant and Toddler Development, third edition, were better for the language-composite component ($P = 0.004$) and for the receptive-communication scale ($P = 0.003$).

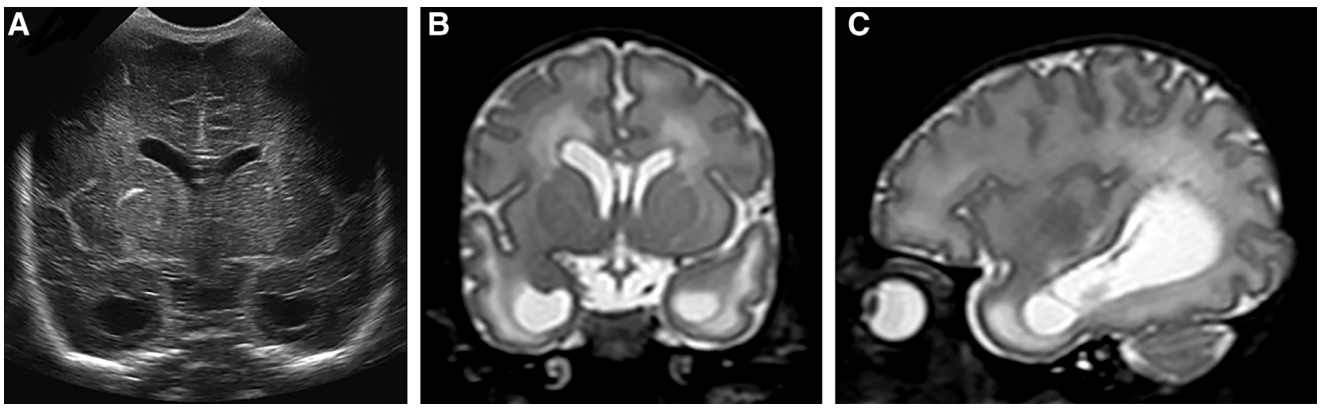

Figure 1 Cranial ultrasound (A) coronal view shows LSV as well as cysts in the temporal lobes. This was confirmed with MRI. The T2 weighted images, coronal (B) and sagittal view (C) do not show the LSV, but confirm the cysts in the temporal lobes as well as increased signal intensity in the temporal lobe and mild ventriculomegaly. LSV, lenticulostriate vasculopathy.

Zika Virus

ZIKV is a mosquito-borne flavivirus, transmitted by the same vector (*Aedes aegypti and aedes albopictus mosquitoes*) as dengue virus and belongs to the family *Flaviviridae*. Although the virus was first reported in the forest in Uganda in 1947, the first major concern was reported when a 20-fold increase in incidence of microcephaly from 2014 to 2015 was noted in Brazil, which public health officials considered to be caused by ZIKV infections in pregnant women.[41] ZIKV infection early in pregnancy carries an increased risk of cell death with dysregulation of cell-cycle progression, resulting in attenuated human neural progenitor cells growth. Dang et al[42] showed that ZIKV attenuates growth in cerebral organoids from human embryonic stem cells due to targeting neural progenitors. ZIKV is able to cross the placenta, especially during the first trimester of pregnancy, and possibly also during the second and third trimesters. The fetus is at increased risk to develop microcephaly or even micrencephaly following ZIKV infection, but imaging abnormalities have also been noted in affected infants who did not develop microcephaly. It has also been shown that ZIKV may be transmitted by sexual transmission and through a blood transfusion.[43,44]

Clinical Symptoms

Clinical symptoms occur in only 20% of the mothers, and consist of fever, a maculopapular rash, arthralgia, and conjunctivitis.[45] These symptoms last for 5-7 days and are usually mild. Guillain-Barré syndrome has also been well-documented in affected adults.[46] In the infected fetus and newborn, 5 features are considered to be unique to congenital ZIKV infection: (1) severe microcephaly with partially collapsed skull; (2) thin cerebral cortex with subcortical calcifications; (3) macular scarring and focal pigmentary retinal mottling; (4) congenital contractures; and (5) marked early hypertonia and symptoms of extrapyramidal involvement.[47]

Diagnosis

The preferred diagnostic test is the PCR. The whole genome of ZIKV has been isolated from the amniotic fluid during pregnancy. Virus-specific IgM antibodies may be detectable >3 days after onset of illness. If there are no detectable virus-specific IgM antibodies in serum collected within 7 days of illness onset, IgM testing should be repeated on a convalescent-phase sample to rule out infection in the mother with a clinical syndrome suggestive of ZIKV infection. After birth fragments of ZIKV genome have been identified in saliva, breastmilk, urine, and serum within several days after delivery, supportive of perinatal transmission.[48] Care should be taken as cross reactivity with dengue viruses, and other flaviviruses (eg, yellow fever and West Nile virus) may cause false positive serological test results.[49]

Imaging Findings

A more severe but otherwise similar spectrum of CNS findings is seen in ZIKV syndrome compared with congenital CMV infection. Due to the severe microcephaly (micrencephaly), the diagnosis is usually made before birth with fetal ultrasound and MRI. Following acute intrauterine arrest in cerebral growth, but not in growth of scalp skin, excessive and redundant scalp skin can be seen. Due to the severe microcephaly the fontanelle is often already closed and the initial postnatal imaging included computed tomography showing punctate calcifications with a typical bandlike distribution, located at the corticomedullary junction. In more than half of the infants, calcifications are seen in the basal ganglia and less often in the thalami. Severe ventriculomegaly was present in almost all infants. It is of interest that occipital cysts that were considered highly suggestive for the diagnosis of congenital CMV infection are also seen in ZIKV infection.[3] Asymmetric calcifications in the cortico-subcortical junction, frontal PMG, mild ventriculomegaly, and delayed myelination have also been reported in normocephalic infants with ZIKV infection.[50] Furthermore progressive ventriculomegaly requiring insertion of a ventriculo-peritoneal-shunt to reduce clinical symptoms can occur in infants with severe microcephaly.[51] A significant decline in infants with ZIKV syndrome in Brazil was noted in 2017 probably due to serological protection from reinfection following ZIKV infection.

Herpes Virus

Neonatal herpes simplex virus (HSV) type 1 and HSV-2 are members of the alpha herpes virus subfamily belonging to the *Herpesviridae* family. HSV infection may occur due to exposure to HSV during the birthing process in a woman with genital HSV infection. When an active genital infection is diagnosed invasive monitoring should be avoided and an elective cesarean section is usually preferred to deliver the infant.[52] An ascending infection is also possible following rupture of membranes. The infection in the mother is usually asymptomatic. Postnatal infection can also be seen following contact with cutaneous herpes lesion in the mother or another caregiver.

Clinical Symptoms

Skin-eye-mouth (SEM) infection is seen in about half of the infants and the other half is either disseminated or restricted to the CNS. Progression to CNS or disseminated disease can occur when a SEM infection is not treated. The symptoms related to the latter type are usually diagnosed at the end of the second week. They may present with feeding difficulties, lethargy, irritability, tense fontanelle, seizures, and even coma. It is important to note that skin lesions are not present in one third of infants with HSV encephalitis.

Diagnosis

The CSF may show pleocytosis, an elevated protein and sometimes a lower glucose level. The diagnosis will be confirmed by isolation of the virus in a cell culture or faster by

HSV DNA by PCR. In 30% of the cases the PCR may not yet be detectable in the early phase of the disease and a lumbar puncture should be repeated when the diagnosis is suspected.

Neuro-Imaging

cUS may show abnormalities in the white matter and central grey nuclei, but abnormalities of the cortex, the cerebellum, and the brain stem may be missed.[53-55] MRI including DWI is now considered the gold standard to assess the brain. In a recent study 3 imaging patterns were recognized, with predominant abnormalities in the watershed distribution, the corticospinal tracts or the frontal/temporal lobe.[56] As could be expected corticospinal tract involvement was significantly associated with poor motor outcome.

Management

Intravenous acyclovir (60 mg/kg/day) should be given when HSV encephalitis is suspected and continued for 3 weeks when confirmed. This drug with the higher dose has reduced mortality (now <10%) as well as morbidity (still 30%-40%). In most centers oral acyclovir will now be administered for 6 months, based on recent data.[57,58] In an infant with HSV-1 encephalitis resistance to acyclovir has been reported due to a mutation in the viral thymidine kinase gene. Vidarabine was added to the treatment with good effect.[59] A repeat lumbar puncture after 21 days of treatment is recommended.

Parvovirus (B19)

Parvovirus B19 virus (B19V) is a small DNA virus belonging to the large *Parvoviridae* family, known to exclusively infect humans. In childhood it is best known as Fifth Disease, presenting with a prodromal phase of fever and flulike symptoms, followed several days later by a "slapped cheek" rash.[60] There are seasonal and annual trends, with outbreaks occurring in the spring in nurseries or schools. B19V infection of human erythroid progenitors in bone marrow can result in cell death, with a transient aplastic crisis. An intrauterine infection therefore, carries a risk of fetal anemia, hydrops fetalis, and fetal death. Fetal demise can be as high as 25% when the infection occurs during the first trimester but was no longer seen after a gestational age of 12 weeks in the study by Al Shukri et al.[61] The risk of hydrops fetalis is highest when the infection occurs during the second trimester.

Diagnosis

About 50% of women of childbearing age are still seronegative. Following the onset of the infection, IgM antibodies are first produced at around 8-12 days, a few days later followed by IgG production. The presence of anti-NS1 antibodies (the main nonstructural protein in B19V) suggests a recent infection.[62] The virus can be detected by performing PCR on a specimen obtained during amniocentesis or cordocentesis.

Imaging Findings

There is limited data on neuro-imaging of infants with prenatal parvovirus B19V infection. Parenchymal calcifications, arterial infarction, and cerebellar hemorrhage have been reported.[63-65]

With increased use of postnatal MRI cortical malformations including hydrocephalus, PMG and heterotopia and cortical dysplasia have been reported.[66-69]

Management

Pregnant women should be aware of any outbreak of B19V at the school or nursery and wash their hands carefully. They will usually get the infection from their own child. Hydrops occurs due to severe anemia and tends to occur in combination with thrombocytopenia. Performing sequential middle cerebral artery peak systolic flow velocity measurements can assess development of in-utero anemia. Treatment is based on cordocentesis transfusion, which may reverse the hydrops with recovery and survival of the fetus. In view of recent data, postnatal MRI and long-term follow-up should be considered especially in severely affected cases that required fetal administration of blood products.

Postnatally Acquired Viral Infections

Parechovirus/Enterovirus

Both EV as well as parechovirus (HPeV) belong to the *Picornaviridae* family, a collection of small nonenveloped viruses with a simple messenger sense RNA genome. The parechoviruses were discovered in 1999 and were originally described as echovirus 22 and 23 within the EV genus (HPeV1 and 2). CNS problems are typically seen following HPeV3 infection.[70,71] They can be acquired prior to but most often following delivery and as their presentation is very similar with regards to clinical symptoms and neuroimaging findings they will be discussed together.[72-74]

Clinical Symptoms

Even though transmission of EV and HPeV from mother to infant is relatively common (30%-50%), encephalitis is more often seen following a postnatal infection, which carries a better prognosis. Disease onset following perinatal transmission is within 1-2 weeks. EV infections are more commonly seen in the summer and fall in temperate climates, while HPeV was encountered in even years in several studies from Europe. Symptoms are variable but fever, irritability, diarrhea, and a rash should alert the clinician. A PCR should be ordered for both EV and HPeV. In a large series by Harvala and colleagues, comparing detection frequencies of EV and HPeV in the CSF in infants presenting with sepsis or CNS symptoms during a 5-year period, HPeV was only seen in infants who were less than 3 months of age and all but 1 had serotype HPeV-3.[75] The absence of pleocytosis can be

misleading. Pleocytosis is more often seen in EV than in HPeV encephalitis.[76] In another study routine screening of EV and HPeV was introduced.[77] In the year following initiation of routine screening, 27 cases of EV and 14 cases of HPeV were identified, compared with 20 cases of EV meningitis and no cases of HPeV during the previous 4-year period. They pointed out that looking at CSF pleocytosis and biochemistry 48.1% of EV and 78.5% of HPeV cases would have been missed. With routine viral screening, the mean length of hospital stay (3.8 vs 5.9 days, $P < 0.001$) and days on antibiotics (2.8 vs 4.7 days, $P < 0.001$) were reduced.[77] A normal early outcome (12 months) was noted in 19 of 26 infants who were less than 90 days old and did not need admission to an intensive care unit but were admitted to a medium care unit with a sepsis like illness (HPeV).[78]

Imaging Findings

Cranial ultrasound may show diffuse echogenicity in the periventricular and deep white matter (Fig. 2). The threshold to perform an MRI should be low in an infant with any of the symptoms mentioned above and is strongly recommended in the presence of seizures. Imaging findings are very similar to findings described below for rotavirus infection. Involvement of the central grey nuclei and the corticospinal tracts (posterior limb of the internal capsule) as well as cystic evolution are more likely to occur in late preterm infants and result in a poor outcome, but in many, mostly full-term infants with DWI abnormalities, restricted to the periventricular white matter without cystic evolution outcomes are better than might be expected.[79] (Fig. 3) In the study by Britton et al.[79] abnormalities extended into subcortical white matter and cortex in 3 out of 9 infants and all 3 had developmental concerns. In a study that compared imaging findings in infants with hypoxic-ischemic encephalopathy and infants with HPeV3 infection, involvement of especially the frontal white matter and the external capsule were significantly more common in those with HPeV3 encephalitis.[80] Intracranial hemorrhage has also been reported in 2 preterm infants with a gestational age of 33 and 34 weeks respectively.[81]

Management

There is no vaccine, and care is primarily supportive, with treatment of seizures, which may be especially difficult to control in HPeV encephalitis. A randomized clinical trial has been performed using oral pleconaril in children with EV sepsis (hepatitis, coagulopathy, and/or myocarditis) with greater survival among the infants treated with pleconaril.[82]

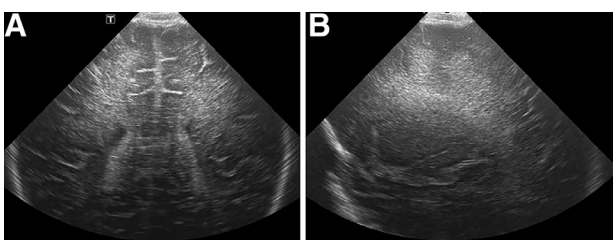

Figure 2 Cranial ultrasound, coronal (A) and parasagittal view (B) showing increased echogenicity in the periventricular and deep white matter in a full-term infant with a HPeV3 encephalitis who presented on day 10 with a fever and developed seizures one day later.

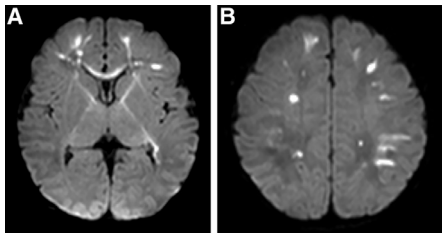

Figure 3 The MRI, DWI, was performed 3 days following onset of symptoms and showed scattered lesions through the white matter, the corpus callosum and milder involvement of the internal capsule and optic radiation on the left side. Outcome assessed with the Griffiths mental development scale at 18 months was within the normal range.

Rotavirus

Rotaviruses belong to the family *Reoviridae* and are nonenveloped double stranded RNA viruses. Rotavirus is the most common cause for gastroenteritis. Even though it is usually benign and self-limiting, it can also result in severe dehydration and even death, and the latter is especially seen in developing countries. Encephalopathy/encephalitis can occur and are well-known severe complications.

Clinical Symptoms

The (near) term infant may present at the end of the first week (day 4-6) with apnea and/or seizures, associated with diarrhea in some but not all.[83] In the absence of diarrhea the stools will sometimes not be cultured with the risk that the diagnosis will be missed. Recent studies suggest that nonstructural protein 4 triggers secretion of proinflammatory cytokines via Toll-like receptor 2. Furthermore, it is possible that peripheral inflammatory cytokines, for example interleukin-6 (IL-6), which is released during the rotavirus infection, could induce IL-6 production in the CNS, resulting in white matter injury.[84] Increased IL-6 levels and interferon-gamma levels were indeed found to be significantly higher in the CSF of patients with rotavirus infection and white matter abnormalities on MRI than in controls.[85] More extensive diffusion abnormalities in the white matter correlated with higher fluid IL-6 levels, suggestive of an inflammatory process in the central nervous system without direct virus invasion.[85]

Several studies from Korea have described clinical symptoms, imaging findings, and recently also neuro-developmental outcome.[86,87] Less than half (43.8%) of the 32 infants studied had a normal outcome, when assessed at 2 years of age with the Bayley scales of Infant Development-II. The diffusion restriction volume percentage was significantly related to cognitive outcome at 2 years, but not with motor

outcome.[88] In the study by Verboon et al 10 out of 13 were (late) preterm and a normal outcome was only seen in the 3 full-term and 1 late preterm infant. Three preterm infants, all with cystic evolution, developed epilepsy, with 2 of these having hypsarrhythmia and all 3 developed cerebral palsy.

Diagnosis

Rotavirus is usually cultured from a stool sample in infants presenting with diarrhea. Even in infants with typical MRI findings (see below) CSF cultures are negative and pleocytosis is not present.

Neuro-Imaging Findings

From around 24-48 hours after the onset of symptoms cranial ultrasound may show diffuse increase in white matter echogenicity. MRI and especially DWI will help to delineate the white matter changes in more detail, with a pattern which is indistinguishable from EV and parechovirus encephalitis (see below). (Fig. 4). Verboon et al [89] were the first to report imaging abnormalities with extensive cystic evolution in preterm infants and predilection for the frontal lobes. In the full-term infants, DWI abnormalities are seen when the MRI is performed within a week following symptom onset and cystic evolution is not as common as in the preterm infant. Cysts will disappear over time, and white matter loss, ex-vacuo dilation and gliosis can be seen during the second year of life.

Management

Universal infant vaccination is now being implemented world-wide, administered orally in 3 doses given with a 4-10 week interval, with the first dose between 6-12 weeks.[90] A reduction in rotavirus related seizures has been reported following rotavirus vaccination.[91,92] The risk of a rotavirus infection in a preterm infant is increased during a rotavirus outbreak, due to a lower level of maternal antibodies against prevalent rotavirus serotypes. As viral shedding may occur following oral vaccination, administration of the vaccine while the infant is still in the neonatal intensive care unit is not recommended. Protection of the preterm population will in time occur over time due to herd immunity.

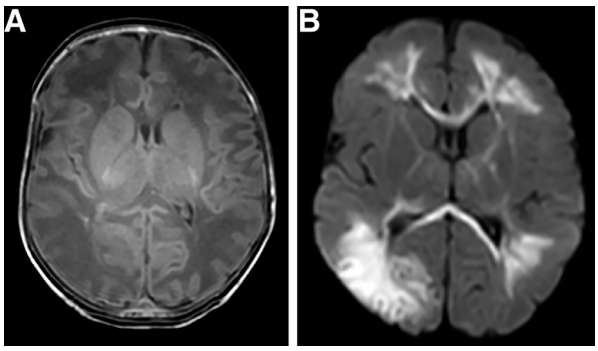

Figure 4 MRI performed 3 days following the onset of symptoms in a 2 week preterm born infant (36 weeks and 5 days). An older sibling had diarrhea. Axial T1 weighted image (A) focal area of increased signal intensity in the right parietal white matter in contrast to the DW image, which shows extensive diffusion restriction in the periventricular white matter, posterior watershed injury on the right and involvement of the corpus callosum and to a lesser extent the PLIC bilaterally. (Courtesy of dr HLM van Straaten, Isala Clinic Zwolle, the Netherlands).

Chikungunya Virus

Another perinatally acquired viral infection, which may result in white matter injury is the chikungunya virus, a mosquito-borne RNA alphavirus genus, belonging to the *Togaviridae* family. The word chikungunya means "bent man" relating to the bent posture due to the arthralgia which is seen in infected adults.

Clinical Symptoms

Signs of infection in the infant may develop during or immediately after delivery, with symptoms occurring in the mother during the week prior to delivery or within 2 days of the delivery 3-12 days following a bite by a contaminated mosquito. Up to 50% of the infants born to a mother with a viremia with exposure to the virus during birth may develop an infection.[93] It will take 3-7 days for the infant to develop symptoms, including poor feeding, diarrhea, a rash, and brown discoloration of the skin, especially of the legs and face.[94] Encephalopathy will occur in about half of the infected infants[95,96], with meningoencephalitis reported in another study between 1%-19%.[93]

Diagnosis

The best way to make the diagnosis is by performing PCR to detect the viral RNA. IgM can also be tested and be detectable from 3-8 days and IgG at 4-10 days following onset of symptoms.

Neuro-Imaging Findings

MRI will show a very similar pattern as in infants with entero- and parechovirus and rotavirus infection, with involvement of the periventricular white matter. In 2 of the 9 infants studied by Gerardin et al, cerebellar hemorrhages were noted as well.[96] In a case series of 38 infants, MRI was performed in 25 with abnormalities of the white matter or intraparenchymal hemorrhages or both in 14.[94] In a follow-up study of 33 children more than half showed global neurodevelopmental delay with microcephaly in 5 and cerebral palsy in 4 children.[97]

Management

There is no vaccine and there are no antiviral agents available. Treatment is based on supportive care.

It is of great interest that viral encephalitis due to different viruses show striking similarities with regard to the

characteristic pattern of white matter injury. It has been suggested that white matter injury following HPeV infection could be attributed to activation of toll like receptor 8 in microglia resulting in injury of premyelinating oligodendrocytes, disturbed axonal development, and neuronal apoptosis.[98] More research is needed to better understand the adverse effect on the brain and especially the white matter, especially in rotavirus infection, where no positive culture or PCR is found in the CSF.

Several other viruses (rubella, varicella zoster, HIV, lymphocytic choriomeningitis virus, West Nile virus) that have not been discussed have also been reported to affect the brain when acquired during pregnancy and/or delivery or after birth.

Conclusions

It is well-known that congenital infections, now also including ZIKV, can have an adverse effect on the brain. We are becoming increasingly aware that perinatally acquired viral infections can also be associated with an adverse neurological outcome. It is not yet fully understood why the white matter is predominantly involved. Prevention is important as therapeutic options are limited.

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