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INVITED REVIEW

Cranial ultrasound in neonatal brain infections

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Abstract

Infection of the neonatal central nervous system (CNS) can cause irreversible brain damage. Cranial ultrasound is an important neuroimaging modality in the neonatal period for detecting brain injury. Several types of organism can cause neonatal CNS infection. The aim of this narrative review is to provide an overview of the most common and typical ultrasonographic features of neonatal CNS infections and their evolution over time. Different microorganisms cause characteristic brain injury patterns. Using numerous imaging examples, we explain the different injury patterns caused by several Gram-positive and Gram-negative microorganisms, fungi, and viruses. This can guide the clinician to appropriate diagnosis and treatment.

Infection of the neonatal central nervous system (CNS) is of major clinical importance as it can cause rapid deterioration and may lead to death or irreversible brain damage. Several types of organism cause neonatal CNS infection, including bacteria, fungi, and viruses. Bacterial infections occur in approximately 0.3 per 1000 neonates,[1–3] with a higher incidence in neonates born preterm. The infections usually cause meningitis, but can also cause empyema, liquefactive necrosis, and brain abscesses. The most common organisms isolated in the newborn period are *Streptococcus agalactiae* (group B *Streptococcus* [GBS]) and *Escherichia coli* (*E. coli*). Other organisms, including Gram-negative enteric bacteria and Gram-positive rods (*Listeria monocytogenes* and *Bacillus cereus*), are rare but can cause severe morbidity and long-term sequelae.[4,5]

Congenital viral infections start in utero and affect the development of the CNS (cytomegalovirus, varicella-zoster virus, zika virus, rubella). Other viruses such as entero-, parecho-, rota-, and herpes viruses can cause aseptic meningitis/encephalitis in the peri- and postnatal periods, leading to neurological symptoms and sequelae.

Lastly, disseminated fungal infections may invade the brain, especially in infants born preterm, causing ventriculitis or disseminated micro-abscesses that coalesce into larger ones. Despite treatment, mortality is high and survivors carry a high risk of neurodevelopmental impairment.[6]

Early recognition with prompt, adequate treatment of neonatal CNS infections is crucial to avoid sequelae or death. A major advantage of cranial ultrasound (CUS) is that it is immediately available and bedside. In this review we focus on the use of CUS in neonatal CNS infection. The primary aim of this narrative review is to give an overview of the most common and typical ultrasonographic features of neonatal CNS infections and their evolution over time. As different

Abbreviations: CSF, cerebrospinal fluid; CUS, cranial ultrasound; DWI, diffusion-weighted imaging; GBS, group B *Streptococcus*; HPeV, human parechovirus; HSV, herpes simplex virus.

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microorganisms have their own characteristic patterns of brain injury, this can guide the clinician to appropriate diagnosis and treatment, which is essential to prevent further complications and improve outcome. For this purpose, we first focus on the general CUS features of CNS infection and then discuss the findings in (1) bacterial infections, (2) fungal infections, and (3) postnatally acquired viral infections. Congenital infections are beyond the scope of this review article and are not discussed.

METHOD

For this narrative review we performed a standard literature search in October 2022 using PubMed and Medical Subject Headings (MeSH terms). A second search was performed in October 2024. The search was carried out with the following MeSH terms ('meningitis' [All Fields] OR 'encephalitis' [All Fields]) AND ('infant' [MeSH Terms] OR 'infant' [All Fields] OR 'infants' [All Fields]) AND ('cranial ultrasound' [All Fields] OR 'cranial ultrasonography' [All Fields]). Case reports, including detailed CUS findings, were also used. This was supplemented by cross-references. In addition, we searched important textbook chapters and review articles for information on neonatal CNS infections ('meningitis' OR 'encephalitis') and neuroimaging findings. No randomized clinical trials were found.

ULTRASOUND IN BACTERIAL CNS INFECTION

For background information on the CUS examination in the newborn infant, including different transducer types, settings, standard planes from the anterior fontanel, and additional windows, we refer to the textbooks and review papers on CUS.[7–9]

Major features of bacterial meningitis can be depicted by CUS (Figure 1).[10] When scanning neonates with (suspected) CNS infection, besides standard planes from the anterior fontanel, additional acoustic windows should be used such as the mastoid fontanel to visualize the infratentorial compartment.[9] Furthermore, the use of a high-frequency linear array transducer enables more detailed visualization of the most superficial parts of the brain such as the cortex and extracerebral fluid compartments.

It is important to perform serial scanning as lesions evolve over time and injury may progress.

Extracerebral spaces

One of the earliest changes in meningitis is oedema. This can be seen on CUS as slit-like ventricles and compression of extracerebral spaces. In addition, the extracerebral spaces and sulci may become hyperechoic and widened owing to arachnoiditis and meningeal inflammation.[11] Both subdural effusion and empyema can develop and these appear as either hypoechoic collections or areas of heterogeneous echogenicity.[12] Empyema is rare: it occurs in about 1% of neonates with meningitis and presents as a fluid collection within the subdural space with sometimes a heterogeneous appearance and mass effect.[10] On the basis of CUS alone, it can be difficult to differentiate between sterile effusion and empyema although a heterogeneous echogenicity and debris are suggestive of the latter.[13–15] While sterile effusion resolves spontaneously, empyema needs aspiration or drainage. Analysis of the fluid confirms the diagnosis.

What this paper adds

- Cranial ultrasound is an important tool in evaluating infection of the neonatal central nervous system.
- Different microorganisms cause characteristic patterns of brain injury.
- Recognition of these patterns on cranial ultrasound helps to enable prompt diagnosis and treatment.

Ventricular system

As mentioned, oedema in the newborn infant with meningitis can present on CUS on the early scans as slit-like ventricles. It is important to be aware that these slit-like ventricles can also be a normal finding in term-born neonates in the first days after birth. However, it is abnormal if it persists or if there are other signs of oedema present such as diffuse echogenicity of brain parenchyma and/or compression of extracerebral spaces.

Another common finding is ventriculitis and inflammation of the choroid plexus (plexitis), represented by an echoic and thickened lining of the ventricular ependyma, the presence of intraventricular strands and debris, and an irregular choroid plexus.[16] Initial slit-like ventricles can widen over time owing to exudate, cerebrospinal fluid (CSF) flow obstruction, and impaired resorption. This may evolve into hydrocephalus, a complication in neonatal meningitis, possibly further complicated by septation and compartmentalization of parts of the ventricular system.[10,12]

Brain parenchyma

Abnormalities in the parenchyma are caused by vasculitis, haemorrhagic and ischaemic infarction, and abscess formation.[17] The lesions are focal or diffuse and often change in appearance over time. Ischaemic stroke, common in GBS meningitis, is initially difficult to detect but usually becomes more apparent when a scan is repeated

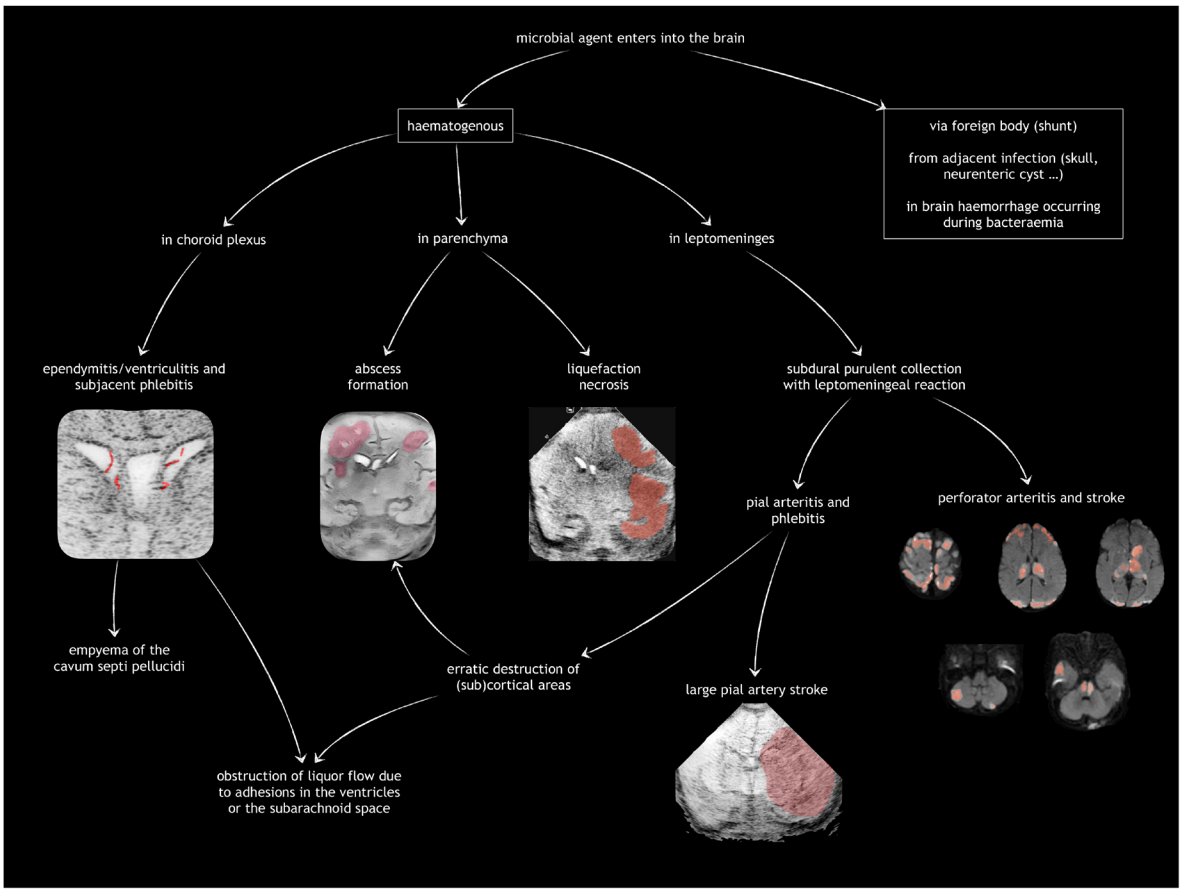

FIGURE 1 The sequence of events in neonatal bacterial brain infection (coloured schemes are inverted images of actual patients).

beyond 48 to 72 hours of admission.[18] Focal infarcts in deep grey matter (perforator stroke) and focal cortical infarctions are typical. In contrast, haemorrhagic necrosis is often detected early as a very irregular area of increased echogenicity.

Brain abscesses are uncommon in neonates; but when they do occur, they are mostly located in the frontal lobes.[19] Usually they start with infarction, then parenchymal necrosis becomes infected and forms an abscess.[17] Haematogenous seeding from neonatal sepsis is another cause of brain abscesses. The lesions can become large, and often there are multiple abscesses. Larger lesions may cause mass effect. Their appearance changes and they become more demarcated over time, with a hyperechoic rim and central echolucency due to liquefaction and cavitation.

Chronic parenchymal changes in neonatal meningitis such as atrophy and cyst formation are visualized with later scans.

Below we discuss the characteristic ultrasound findings of the most common organisms associated with neonatal bacterial CNS infection. This is also summarized in Table 1.

Table 2 provides the most important aspects on the timing of neuroimaging for different microorganisms. In general, an early/admission CUS scan should be performed in every newborn infant with (suspected) meningitis. Subsequently, serial scanning should be performed as some lesions may become more distinct over time and for some microorganisms brain lesions may progress rapidly. Longer follow-up scanning can be important to screen for cyst formation and atrophy, and in some specific microorganisms also to detect (late) hydrocephalus.

GBS

GBS (Figures 2–4), a beta-haemolytic Gram-positive coccus, is a leading cause of neonatal meningitis. Infections can be of early or late onset. Typically, the newborn infant acquires infection perinatally by vertical transmission. Late-onset GBS infection, after day seven, is often acquired from human contact or nosocomial horizontal transmission.[20] The incidence of early-onset GBS sepsis and meningitis in neonates declined over the past two decades, owing to the use of intrapartum prophylaxis. Despite this decline it is still the most common cause of bacterial meningitis in neonates, occurring in 0.17 to 3 per 1000 live births.[21–23] The mortality rate of neonatal GBS meningitis ranges between 10% and 15%.[17] Long-term sequelae such as cerebral palsy, developmental delay, epilepsy hydrocephalus, and visual and hearing impairment are recorded in 20% to 40% of the survivors.[24]

TABLE 1 Characteristic brain injury patterns on neuroimaging for different microorganisms involved in neonatal central nervous system infection.

Microorganism	Neuroimaging pattern
Bacterial	
Group B *Streptococcus*	Stroke-like pattern, asymmetric distribution. Perforator stroke in basal ganglia and/or thalami. Cortical stroke. Can also lead to ventriculitis and hydrocephalus.
Escherichia coli	Ventriculitis, adhesions, (late) hydrocephalus, isolated parts of the ventricular system; isolated fourth ventricle.
Other Gram-negative enteric bacteria *Citrobacter*, *Serratia*, *Enterobacter*, *Proteus* species	Haemorrhagic necrosis, predilection frontal lobes but also other brain regions; asymmetric distribution. Can lead to severe destruction of brain tissue and abscess formation.
Bacillus cereus	Liquefactive necrosis in periventricular and subcortical white matter with irregular border, and asymmetrical distribution. Followed by cystic degeneration.
Streptococcus pneumoniae *Haemophilus influenzae*	Subdural effusion, empyema; (late) hydrocephalus.
Listeria monocytogenes	Preterm birth. Intraventricular haemorrhage and white matter injury common. Can also lead to small granulomatous lesions in the brain.
Staphylococcus aureus	Micro-abscesses.
Fungal	
Candida species	Diffuse micro-abscesses in periventricular and subcortical white matter, deep grey matter, cerebellum, and brainstem. Can be followed by central cystic degeneration and/or glial scarring. May also evolve into macro-abscesses and/or cause late hydrocephalus.
Viral	
Enterovirus, *Parechovirus*, *Rotavirus*	Periventricular (frontal) white matter. Starts as increased echogenicity and may show cystic evolution over time, especially in those born (late) preterm.
Herpes simplex virus	Cortical lesions in temporal and frontal lobes; may also affect deep grey matter corticospinal tracts, cerebellum, and brainstem.

Neonatal GBS meningitis can be complicated by cerebral arterial involvement. Two distinct patterns of focal infarction are recognized: (1) perforator arterial stroke in the basal ganglia and thalami and (2) focal cortical infarction. These patterns can be present in an asymmetric distribution and in complex combinations.[18–25] On early scans the lesions are subtle and difficult to recognize unless there also is haemorrhagic transformation. Serial CUS during the first week after the onset of symptoms shows an increase in echogenicity in the affected area(s) with a more prominent appearance of deep grey matter abnormalities and abnormal demarcation of the grey–white matter junction in areas with cortical infarction. Over the next 2 to 4 weeks volume loss and cavitation of affected areas may develop.

Other CUS abnormalities include subdural effusion appearing as enlarged hypoechoic concave extracerebral spaces, signs of meningeal inflammation with echogenic lining of the cortical surface and widening of the sulci, and signs of ventriculitis with lining of the ventricular wall and strands and debris in the lateral ventricles. Subdural empyema and development of hydrocephalus also occur in GBS meningitis but less often than other pathogens such as *E. coli* (below).[26]

E. coli

E. coli (Figure 5), a Gram-negative rod-shaped bacterium, is the second most common cause of neonatal meningitis. The overall mortality rate of *E. coli* meningitis is high and varies between 10% and 15%.[27–29] The risk of ventricular dilatation is high, occurring in 25% to 50% of affected infants. Ventricular dilatation can already be seen in the acute phase of the meningitis owing to an increase in CSF production because of inflammation at the choroid plexus and reduced CSF resorption. Associated intraventricular haemorrhage in infants born preterm sometimes contributes to the ventricular dilatation. During the first days, debris may develop inside the ventricular system. This can be visible on CUS, for example in the occipital horns of the lateral ventricles, as a collection of slightly hyperechoic material. Intraventricular adhesions can follow. These strands contribute to CSF flow impairment, sometimes leading to entrapment of ventricle compartments. A typical form of entrapment in *E. coli* meningitis is isolation of the fourth ventricle owing to obstruction of both its inflow and outflow pathways. In situations with a trapped fourth ventricle, the dilatation can result in high pressure on brainstem and cerebellum. Prompt recognition is important for appropriate surgical intervention.[30,31] Ventricular dilatation can still develop weeks after the initial infection, even as late as 6 weeks after discontinuation of a complete course of antibiotics. It is therefore crucial to perform follow-up CUS scans and head circumference measurements until at least 8 weeks after onset of infection.

TABLE 2 Important aspects of timing of neuroimaging for different microorganisms involved in neonatal central nervous system infection.

Microorganism	Aspects in timing of neuroimaging
Bacterial	
Group B *Streptococcus*	Stroke-like pattern. Discrete on early CUS scan. More distinct after 48–72 hours. Cortical infarction can be missed on CUS (use linear high-resolution transducer). Diffusion-weighted MRI <7 days important for full extent of injury and involvement corticospinal tract.
Escherichia coli	Ventriculitis, adhesions, (late) hydrocephalus. May develop in acute stage of infection. May also develop weeks after treatment. Perform follow-up CUS scans and follow head circumference until at least 2 months after the infection.
Other Gram-negative enteric bacteria (*Citrobacter*, *Serratia*, *Enterobacter*, *Proteus* species)	Haemorrhagic necrosis. Present on early CUS scan as inhomogeneous increased echogenicity. Frequent CUS follow-up after onset of symptoms required. Spreads rapidly to other brain areas; leads to early destruction of brain tissue, abscess formation.
Bacillus cereus	Liquefactive necrosis. Seen on early CUS scan as inhomogeneous increased echogenicity, irregular demarcation. Followed by rapid tissue loss and cystic degeneration.
Streptococcus pneumoniae, *Haemophilus influenzae*	Subdural effusion, empyema, hydrocephalus. May also develop weeks after treatment. Perform follow-up CUS scans and follow head growth until at least 2 months after the infection.
Fungal	
Candida species	Micro-abscesses. Often already seen at onset of illness. May progress during treatment. Diffusion MRI important to show full extent of (active) lesions. May evolve into macro-abscesses and/or cause late hydrocephalus. Perform follow-up CUS and follow head growth until at least 2 months after the infection.
Viral	
Enterovirus and *Parechovirus* *Rotavirus*	Periventricular white matter echogenicity. May be discrete on early CUS scan. More distinct after 48–72 hours. Diffusion-weighted MRI within 7 days important, shows very distinctive pattern with/without involvement corticospinal tract. Follow-up scanning 2–4 weeks for cystic evolution.
Herpes simplex virus	Cortical lesions. Small lesions can be missed by CUS. Diffusion-weighted MRI <7 days to assess full extent and involvement corticospinal tract. Follow-up scanning 2–4 weeks for cystic evolution and atrophy.

Abbreviations: CUS, cranial ultrasound; MRI, magnetic resonance imaging.

Other Gram-negative bacteria

Other Gram-negative bacteria (Figure 6) causing neonatal meningitis include *Citrobacter*, *Serratia marcescens*, *Proteus*, *Pseudomonas*, and *Enterobacter* species. Characteristic of these organisms is that they can cause rapid and severe cerebral destruction. Partly affected areas can subsequently form abscesses mainly but not exclusively in the frontal lobes.[19,32]

Citrobacter koseri preferentially causes brain abscesses. This Gram-negative bacillus from the Enterobacteriaceae family is responsible for fewer than 5% of all cases of neonatal meningitis and rarely affects infants older than 8 weeks. However, it leads in 75% of all cases to the formation of brain abscesses. Abscesses due to *C. koseri* develop from severe haemorrhagic necrosis into liquefaction.[33–35] The evolution of a brain abscess can be followed by serial CUS. Early ultrasound often already shows typical irregular, asymmetric areas of increased echogenicity within the white matter. Owing to lesion swelling there may be a mass effect on the surrounding brain tissue. On follow-up scans the centre of the lesions becomes echolucent, with a hyperechoic rim. As liquefaction of affected areas progresses, sometimes with rupture into the ventricles, extensive parenchymal destruction is possible. Within these areas some hyperechoic debris may remain visible.[12] Pneumocephalus, intracranial air or gas collection, associated with neonatal meningitis has been observed in neonatal *C. koseri* meningitis.[36]

Serratia marcescens, belonging to the family Enterobacteriaceae, is also a cause of meningitis, and outbreaks of *Serratia* species in neonatal intensive care units have been reported. Complicated bacterial meningitis with extensive haemorrhagic necrosis of cortex and white matter is characteristic. Again, this can lead to the formation of abscesses that may initially show as (multiple)

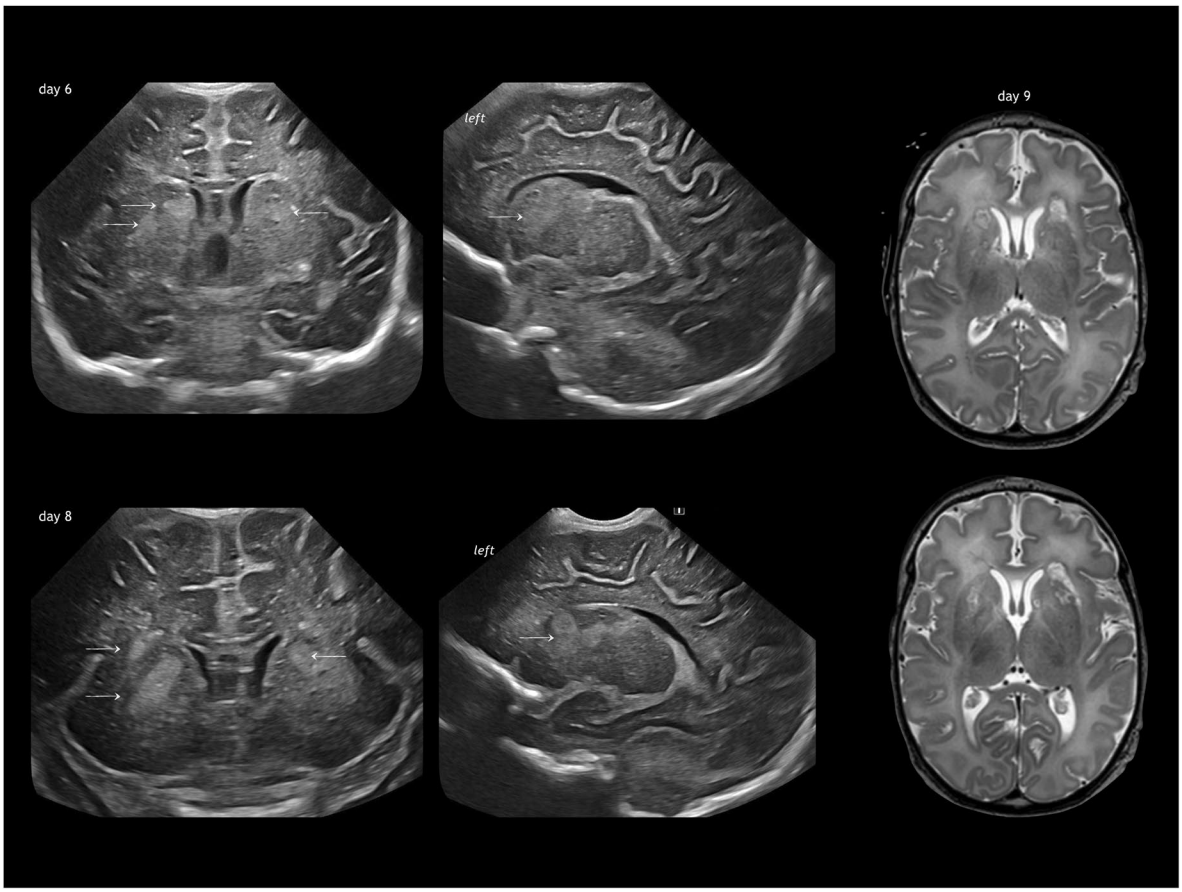

FIGURE 2 Early-onset group B *Streptococcus* meningitis: multiple arterial striatal perforator strokes in a term infant presenting with seizures and fever on postnatal day 6. Observe increase of echogenicity and sharper delineation of ischaemic areas in caudate head and putamen between day 6 and day 8 (arrows). T2-weighted magnetic resonance image on day 9 illustrates the non-haemorrhagic character of the juxtaventricular striatal lesions.

round lesions with central echolucency, an echogenic border, and strands. Subsequent liquefaction can evolve into larger cavitations, still having some mass effect on the surrounding tissue.

Proteus mirabilis and *Enterobacter* species are even less common but can result in similar abscess formation.[37,38]

In meningitis with Gram-negative bacteria, CUS is an important diagnostic tool: serial scanning facilitates recognition of liquefaction and abscess formation. This is important to guide treatment. When abscesses become larger than 2.5 cm in diameter, neurosurgical intervention may be warranted.[39,40]

Bacillus cereus

Bacillus cereus (Figure 7) is a common Gram-positive food bacterium. Although a rare cause of meningitis in neonates, it can have devastating consequences.[41] The organism itself swarms out from vessels into tissue where its toxins cause liquefactive necrosis. On CUS widespread irregular areas of echogenicity of the periventricular and subcortical white matter can be seen. These abnormalities tend to be asymmetrical and may take a cauliflower appearance. Typically, the grey matter seems primarily spared. Serial scanning depicts central necrosis with subsequent cyst formation in hours to days.[42]

Streptococcus pneumoniae and Haemophilus influenzae

Streptoccus pneumoniae as well as *Haemophilus influenzae* infections are uncommon in the neonate. One of the characteristic features is subdural effusion, which is relatively rare with neonatal CNS infection by other organisms.[43] On CUS there can be a circumscript biconvex hyperechoic collection within the extra-axial space with some mass effect on the underlying tissue. Echo reflections in the collection may be seen. Most commonly the effusions are reactive and sterile; empyema may also develop.[13]

Listeria monocytogenes

Listeria monocytogenes (Figures 8), a Gram-positive non-spore-forming rod, is a relatively rare cause of meningitis with an incidence of 0.61 per 100 000 live births.[44] It

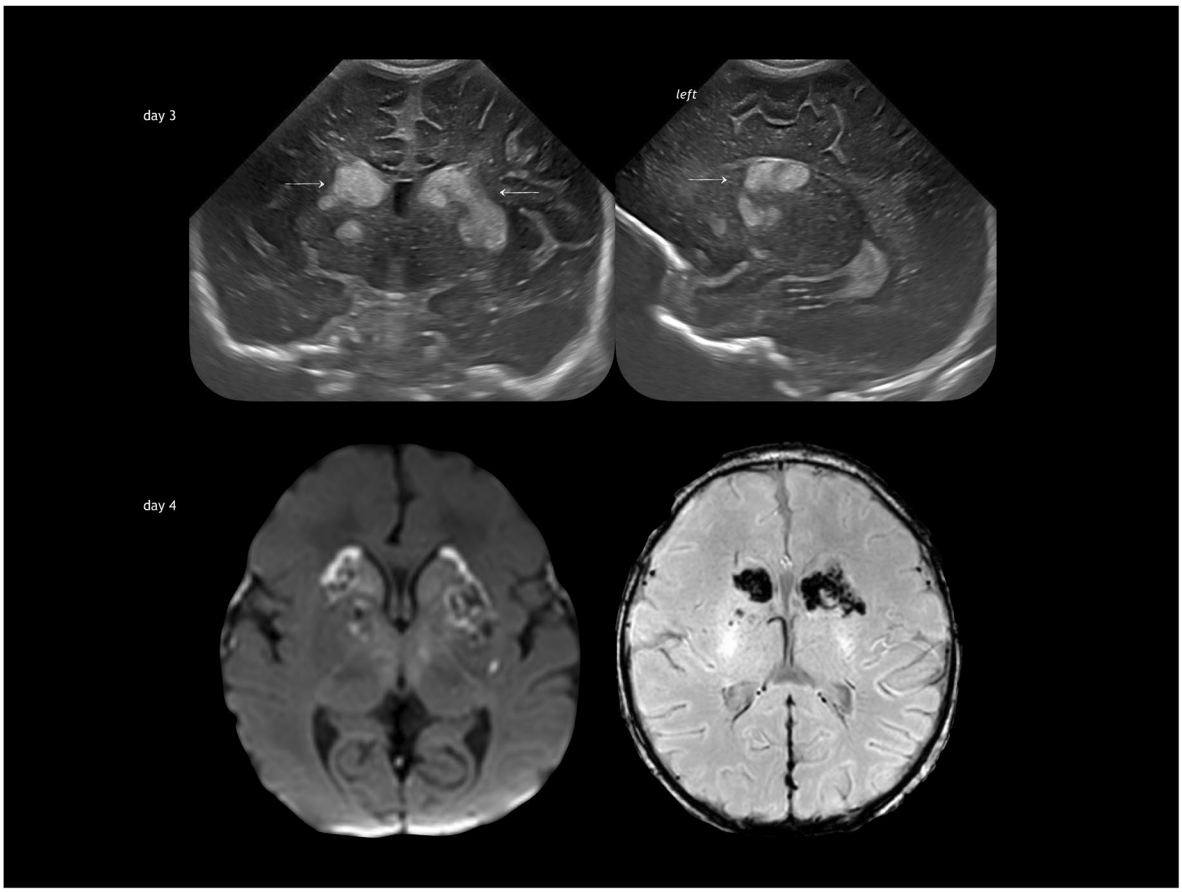

FIGURE 3 Early-onset group B *Streptococcus* meningitis: ischaemic perforator strokes with haemorrhagic conversion (arrows) in an infant born at term with seizures and documented meningitis on day 3. Below the corresponding magnetic resonance image at day 4. Diffusion-weighted imaging (left) and susceptibility-weighted imaging (right) confirming the stroke lesions with haemorrhagic conversion.

is related to food contamination, especially unpasteurized dairy products, soft cheeses, and ready-to-eat meals. Infection of placenta and fetus can lead to spontaneous abortion or preterm birth.[45] Early-onset infection presents as pneumonia, septicaemia, and meningitis with high fatality rates of 14% to 56%. When the neonate is infected during labour or after birth, symptoms may only present 8 to 30 days after birth. Late-onset infection can result in meningitis.[46] The microorganism causes small miliary lesions in many organs, including the brain. These lesions develop into necrotizing granuloma ('granulomatosis infantiseptica'), detected as multiple small hyperechoic spots, localized particularly in the ventricular wall, choroid plexus, and the meninges. These granulomata may become multiple small abscesses, rendering effective treatment difficult.

Staphylococcus aureus

Infected micro-emboli may find their way into the brain in ongoing *Staphylococcus aureus* bacteraemia, sometimes resulting in isolated typical abscess formation (Figure 9).

ULTRASOUND IN FUNGAL CNS INFECTION

Intracranial fungal infections may be encountered in extremely preterm neonates, with an incidence ranging from 0.4% to 1.1% of these infants admitted to a neonatal intensive care unit.[47] *Candida* species are the most common neonatal fungal CNS infection. Other species such as *Cryptococcus* or *Aspergillus* (Figure 10) can cause meningitis but this is extremely rare.[48] Because of that low prevalence we only discuss *Candida* species.

Candida

There are different *Candida* species (Figure 11) such as *Candida albicans*, *Candida glabrata*, and *Candida krusei*. Most invasive *Candida* infections in neonates are caused by *C. albicans*. In neonates born preterm, systemic candidiasis usually occurs between 2 weeks and 6 weeks after birth. Symptoms are similar to bacterial septicaemia and include apnoea, temperature instability, lethargy, hypotension, and hyperglycaemia. *Candida* meningitis usually occurs

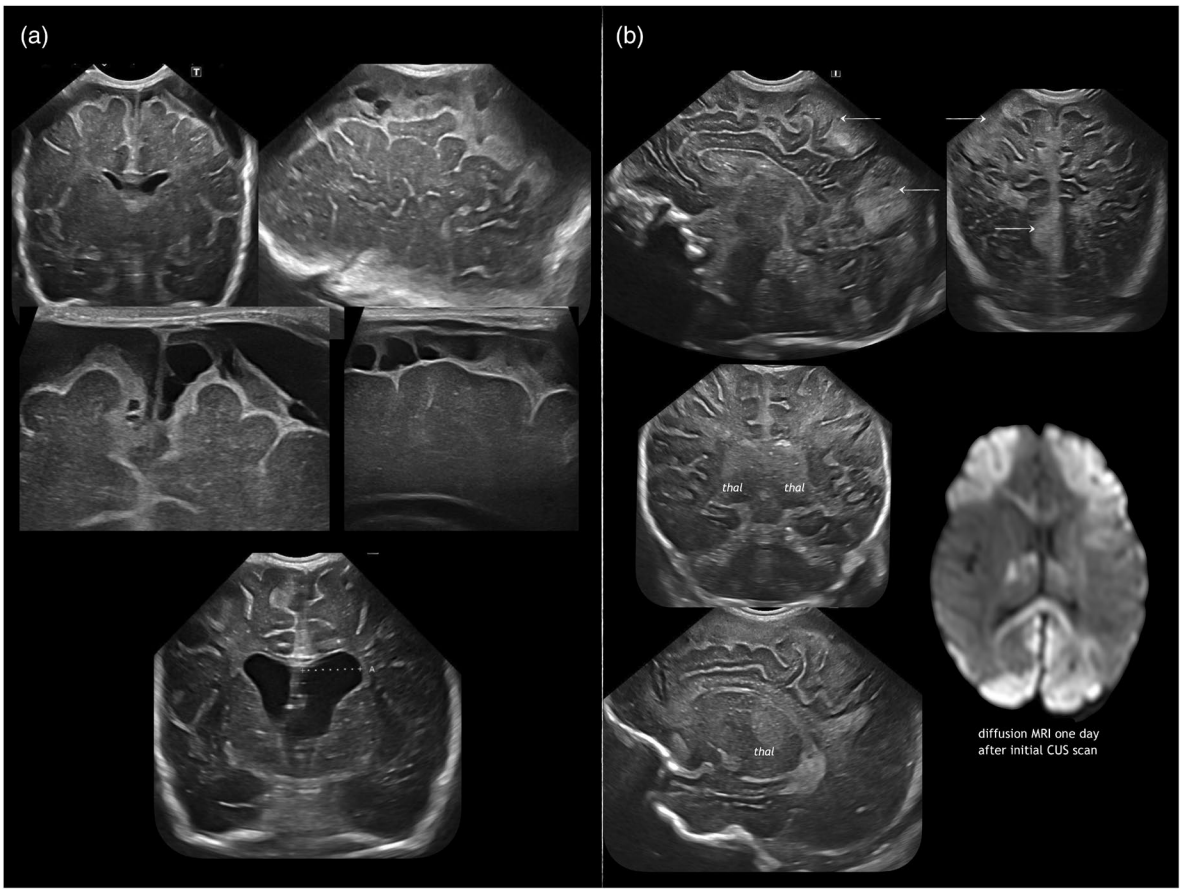

FIGURE 4 Late-onset group B *Streptococcus* meningitis: leptomeningitis with subcortical infarction. (a) Infant born late preterm with late-onset GBS meningitis, prolonged antibiotic therapy; (sub)acute images: extensive subdural collections, arachnoiditis and meningeal thickening; cranial ultrasound at term (below) shows resolution of the subdural collections and ventricular dilatation which stabilized spontaneously afterwards. (b) Term-born infant with late-onset GBS meningitis: on day of admission hyperechoic inflammatory collections are suspected in and around the frontoparietal and occipital cortex, there is an increase of echogenicity in both thalami; the diffusion-weighted MRI (right) confirms the stroke-like lesions in the cortex and both thalami. Abbreviations: GBS, group B *Streptococcus*; MRI, magnetic resonance imaging; thal, thalami.

as manifestation of disseminated candidiasis, in which context it is reported in 10% to 25%.[17] The small size of the microorganism allows access to the microcirculation.[49,50] Serial CUS is important for recognition and follow-up of CNS involvement in systemic infection.[51,52] The most common and typical CUS findings are scattered small round hyperechoic micro-abscesses in subcortical, periventricular, and deep grey matter and sometimes also in cerebellum and brainstem.[53] These lesions are confluent and form macro-abscesses, with mass effect and often with a hypoechoic centre. Another feature is ventriculitis, showing as a hyperechoic ventricle wall, intraventricular septae, and debris in the ventricles and posterior fossa CSF spaces. Sometimes ventriculitis and meningitis lead to obstructive hydrocephalus.

ULTRASOUND IN VIRAL CNS INFECTION

Perinatal viral infections are less common than bacterial infections, but they can cause severe brain injury.[54] The incidence rate for enterovirus and human parechovirus (HPeV) meningitis ranges from 0.04 to 0.77 per 1000 live births.[55,56] The prevalence of different pathogens varies in different countries. Most common worldwide are HPeV, enterovirus, rotavirus, and herpes simplex virus (HSV) infections.[57] Viral infection most commonly affects the white matter, in a symmetrical pattern and with a predilection for the frontal lobes.

Enterovirus/parechovirus

Infections with enterovirus and HPeV (Figure 12) can be mild and self-limiting but may also run a fulminant course. Encephalitis is more commonly seen caused by enterovirus than HPeV, but the latter may run a more severe course. As clinical presentation and neuroimaging findings are similar, the two are discussed together. Enterovirus and HPeV are small non-enveloped RNA viruses and belong to the Picornaviridae. They are subdivided into several serotypes. HPeV type 3 is associated with neonatal encephalitis. Neonates can be admitted with fever, rash, irritability, feeding problems, and/or diarrhoea. Group B coxsackie virus and echovirus 11 are often associated with systemic neonatal

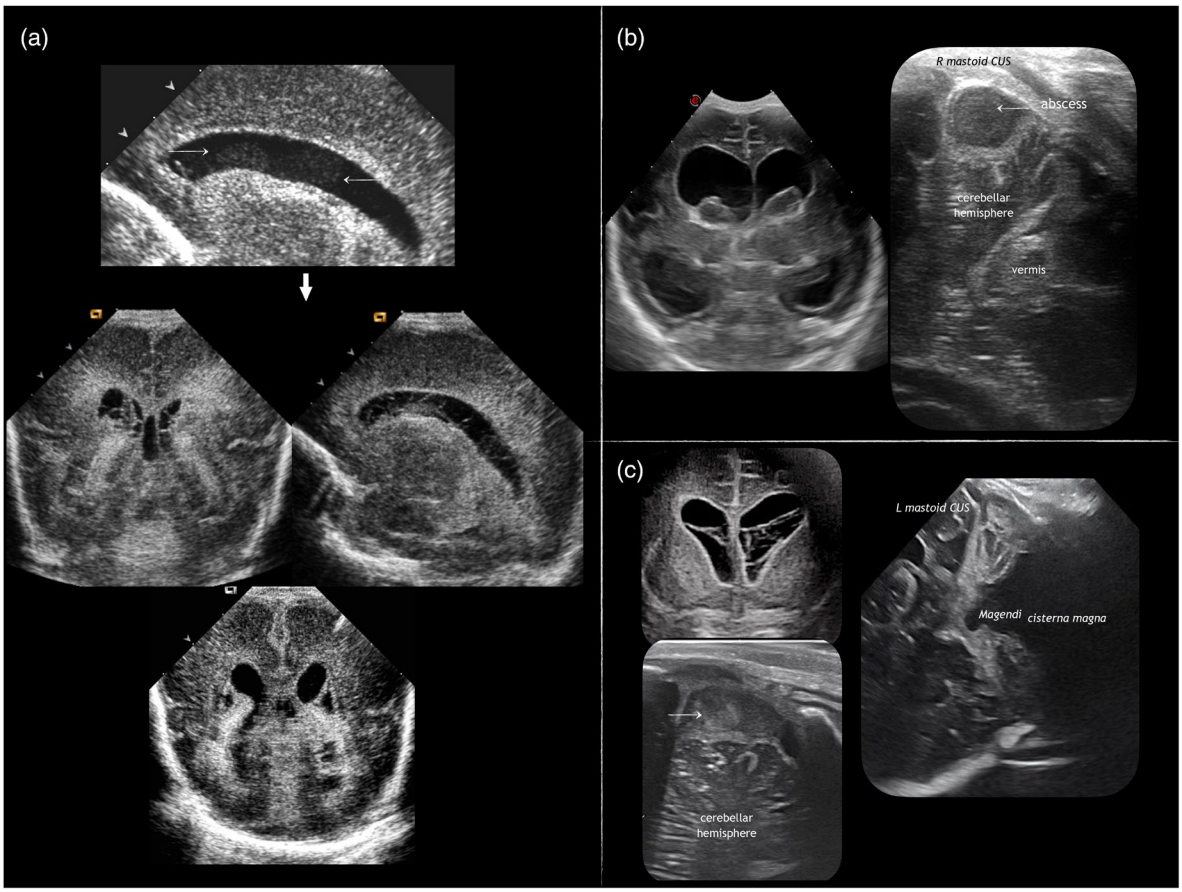

FIGURE 5 *Escherichia coli* meningitis and ventriculitis. (a) Infant born preterm (gestational age 26 weeks) with initial IVH grade 2, subsequent *E. coli* ventriculitis around day 5: evolving intraventricular changes, at first only faintly hyperechoic conglomerates, later adhesions (strands) and compartmentalization of the ventricle cavities. (b) Infant born preterm (gestational age 30 weeks) with initial IVH grade 3, subsequent *E. coli* ventriculitis around day 14 with abscess formation over the cerebellar surface as seen on a right mastoid fontanel view; observe dilatation of the lateral and third ventricles, sparing the fourth ventricle. (c) Infant born preterm (gestational age 35 weeks) with intraventricular strands, a collection of debris around the cerebellum on the mastoid fontanel view (arrow) and an enlarged foramen of Magendi and cisterna magna (pericerebellar arachnoid pathways hindered by inflammation). Abbreviations: CUS, cranial ultrasound; IVH, intraventricular haemorrhage; L, left; R, right.

infection, and myocarditis is a well-known complication.[58,59] Most neonates acquire the infection in the perinatal period from a symptomatic mother or sibling. Perinatally acquired enterovirus and HPeV infection have their clinical onset between postnatal days 3 and 7.[45] For both enterovirus and HPeV encephalitis, CUS can show similar abnormalities with diffuse periventricular hyperechogenicity, resembling extensive periventricular leukomalacia.[60] Involvement of the external capsule and the frontal white matter can be seen, especially in HPeV3.[61–63] Cystic evolution may ensue and can be detected by serial CUS; it is therefore important to perform serial scanning. Cysts are more likely to develop in infants born (late) preterm than the term neonates.[64] In case of cystic evolution, the infant is more likely to have a poor neurodevelopmental outcome.[65,66]

Rotavirus

Rotavirus (Figure 13) is a non-enveloped double-stranded RNA virus that belongs to the family Reoviridae.[45] Although most infected infants are thought to present with gastro-enteritis, in neonates this only occurs in 20%.[67–69] Rotavirus can be detected in the stool, even in the absence of diarrhoea. In cases with rotavirus encephalitis, investigation of the CSF is usually normal, without pleocytosis or positive culture, and only in a few reports was the polymerase chain reaction for rotavirus weakly positive.[68] Therefore, the diagnosis is often based on a typical clinical presentation together with the imaging appearance and detecting the virus in the stool. In recent years rotavirus has increasingly been reported as a possible cause of neonatal seizures and encephalitis. It typically presents on day 4 to 6 and can be the cause of so-called 'fifth day seizures'.[67]

CUS can show hyperechogenicity of the white matter from around 24 to 48 hours after symptom onset.[66] The hyperechogenicity may evolve into cysts over time and, similar to entero- and parechovirus, is more likely to do so in infants born late preterm than in infants born at term. There is a predilection for the frontal lobes. Magnetic resonance imaging (MRI) is of additional value as it clearly shows the extent of

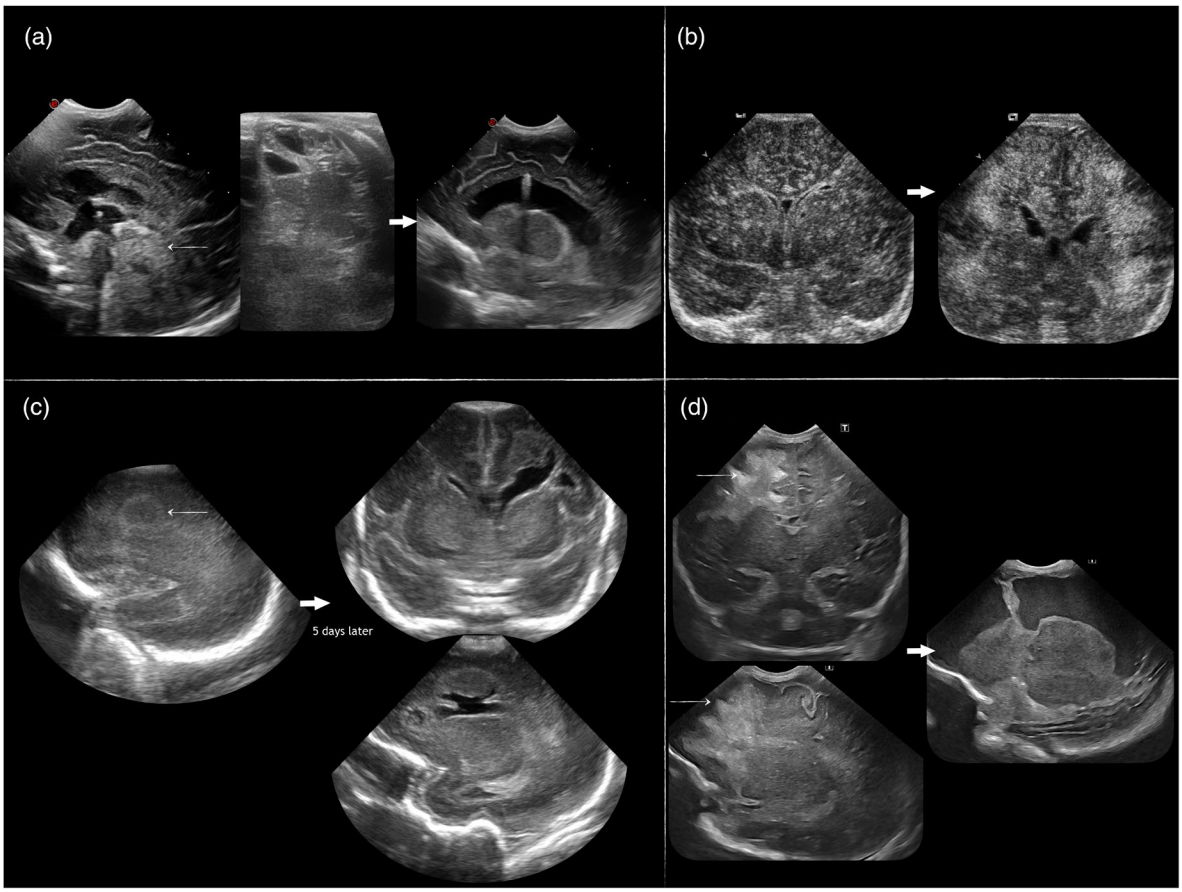

FIGURE 6 Enterobacterial meningitis. (a) Infant born preterm (gestational age 32 weeks) with Enterobacter septicaemia, fasciotomy for necrosis of a foot, thrombocytopenia. On a midsagittal cranial ultrasound view from the anterior fontanel the upper vermis margin is obscured initially (arrow); mastoid insonation (middle) reveals intraparenchymal cerebellar destruction on serial imaging with membrane formation; the process ends in triventricular hydrocephalus necessitating placement of a reservoir for ventricular tapping (right image). (b) Infant born very preterm with Pseudomonas septicaemia and extensive microabscedation of the entire brain preceding total destruction before demise; this proceeds in less than 2 weeks. (c) Infant born preterm (gestational age 26 weeks), day 15: *Serratia marcescens* sepsis and meningitis; parenchymal circular hyperechoic change evolves into cavitation in 5 days. (d) *Citrobacter* encephalitis in a term infant: asymmetric, focal hyperechoic change of white matter and striatum evolves into extensive liquefactive necrosis of the entire parenchyma within a few days.

white matter involvement, especially when performed early using diffusion-weighted imaging (DWI). There are multiple small studies that have reported symmetrical diffusion restriction in the white matter. Although the appearance is similar to cystic leukomalacia, the white matter abnormalities may extend more into subcortical white matter.[66,70]

HSV

HSV (Figure 14) types 1 and 2 are large enveloped virions with double-stranded DNA and are a member of the family Herpesviridae.[45] About 85% of the infants with herpes infection acquire it peripartum. Transplacental infection is rare (5%) and is not discussed in this paper. Postnatal infection can occur and is almost always caused by HSV type 1.[17]

There are three forms of presentation of perinatal HSV infection, which can coexist: skin–eye–mouth, meningoencephalitis, and disseminated disease. Neonatal HSV meningoencephalitis usually presents between the second and third week up to the sixth postnatal week. CUS may show parenchymal changes but is likely to miss small cortical lesions. It is therefore recommended to document lesions with MRI.[71] In adults, herpes encephalitis follows a retrograde axonal pathway from the oropharyngeal mucosa, and typically affects the medial temporal lobes, frontal lobes, and the limbic system sparing the basal ganglia. Neonatal HSV encephalitis is typically haematogenous, and has a more variable imaging appearance. It can be multifocal or only limited to the thalamic region, the corticospinal tract, the frontal lobes, or the cerebellum.[72,73] Lesions can be both ischaemic and haemorrhagic. Near-total cerebral mantle destruction has been reported on several occasions.

MRI IN NEONATAL CNS INFECTION

Although CUS often provides the clinician with important early diagnostic information, it can be challenging to investigate brain lesions by ultrasound alone. Therefore at least

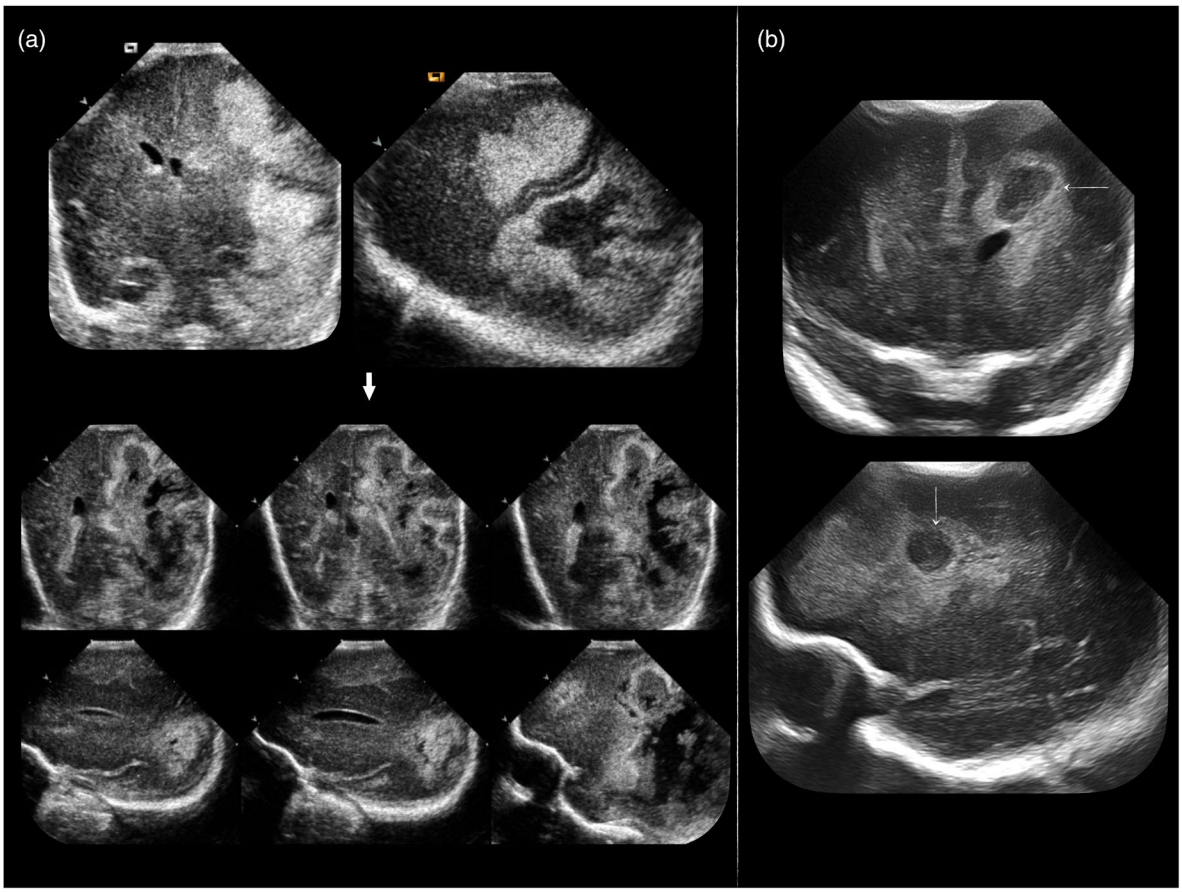

FIGURE 7 *Bacillus cereus* meningo-encephalitis. (a) Infant born preterm (gestational age 30 weeks) with sepsis screen 48 hours before; lethargic, and full fontanelle but normal cerebrospinal fluid findings; cranial ultrasound shows predominantly unilateral extensive and irregular white matter echogenicity followed by destruction in the week after detection; the causative organism turned out to be *Bacillus cereus*. (b) Infant born preterm (33 weeks postmenstrual age) with *Bacillus cereus* in blood and cerebrospinal fluid: predominantly unilateral frontal white matter destruction.

one MRI scan should be performed in every neonate with a complicated meningitis, so every neonate presenting with acute neurological symptoms such as seizures, abnormal ultrasound findings, and/or with signs of ongoing infection despite treatment, provided the infant is stable enough to be transported to the MRI unit. In a recent study it was shown that infants with abnormal CUS findings, especially during the post-acute phase of bacterial meningitis, had the highest risk of sequelae.[74] MRI will show the extent and location of both acute and chronic stages of injury in detail and helps to assess areas difficult to visualize with ultrasound. Another useful feature of MRI is the combination of different diagnostic sequences. DWI sequences are an important part of the protocol within 1 week of onset, when DWI is sensitive to detection of ischaemic lesions, compared with conventional T1- and T2-weighted images. This is helpful, for example, in infants with GBS meningitis where DWI can show a very characteristic pattern of stroke-like lesions in the cortex and/or deep grey matter.[18] In neonates with meningitis/meningoencephalitis caused by entero-, parecho-, and rotaviruses, early DWI reveals a characteristic pattern of restricted diffusion in periventricular white matter (with frontal predilection), corpus callosum, and optic radiation.[75] These changes may precede cysts, which may be extensive. With herpes encephalitis, conventional MRI can be normal in the early stage of the infection, but DWI can already highlight areas of diffusion restriction in the cortex.[71,76] DWI abnormalities in the corticospinal tract can also be documented, although with infection the prognostic relation of this to motor outcome is less strong compared with hypoxic–ischaemic brain injury.[77] Finally, DWI can show enhancement in areas with abscess formation and empyema.[78] Other sequences are added on indication, for example MR venography when complications such as sinovenous thrombosis are suspected.

LIMITATIONS

The aim of this narrative and pictorial review has been to give an overview of the most common and typical ultrasonographic features of neonatal CNS infections and their evolution over time. The search strategy was therefore not as rigorous as that of a systematic review. This may have caused a selection bias in the studies that were used, and some relevant studies may have been missed. However, we feel that the description of distinctive ultrasound features, together

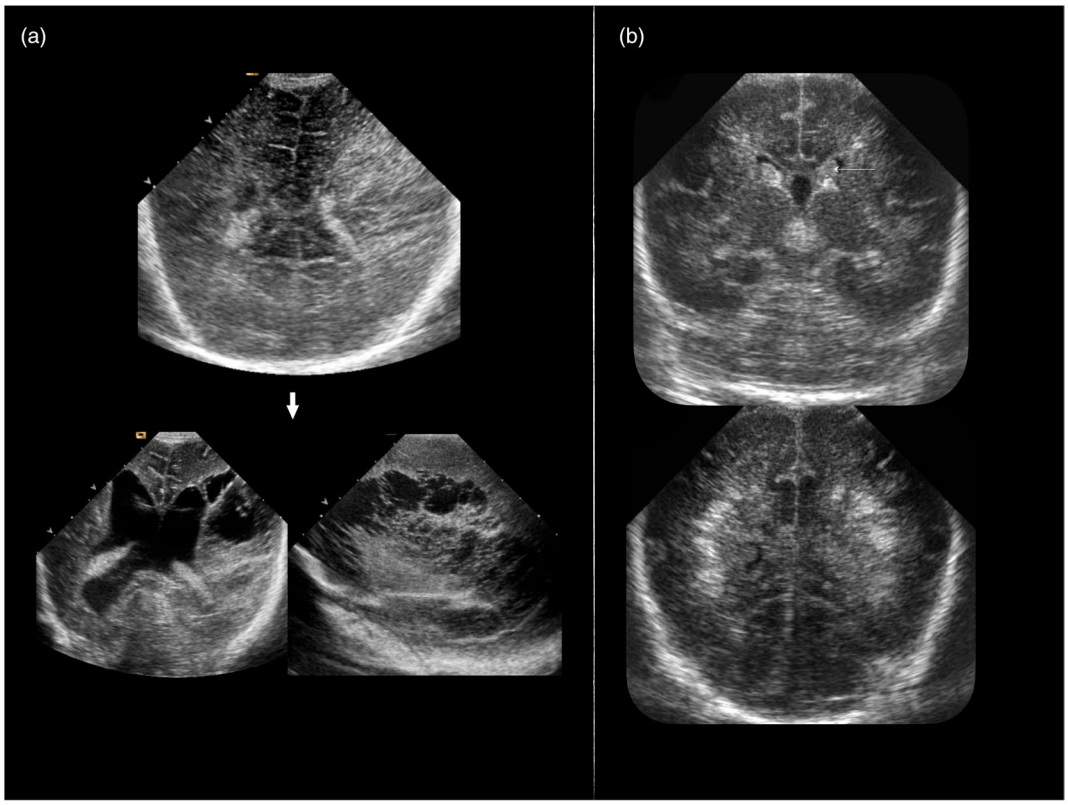

FIGURE 8 *Listeria* encephalitis. (a) Medial cerebral artery stroke complicating *Listeria* septicaemia in a term infant with subsequent tissue loss on follow-up imaging (4 weeks). (b) Bilateral parietal hyperechoic white matter change with radial character in listeria infection in an infant born preterm; observe additional inflammatory changes in plexus choroideus (arrow).

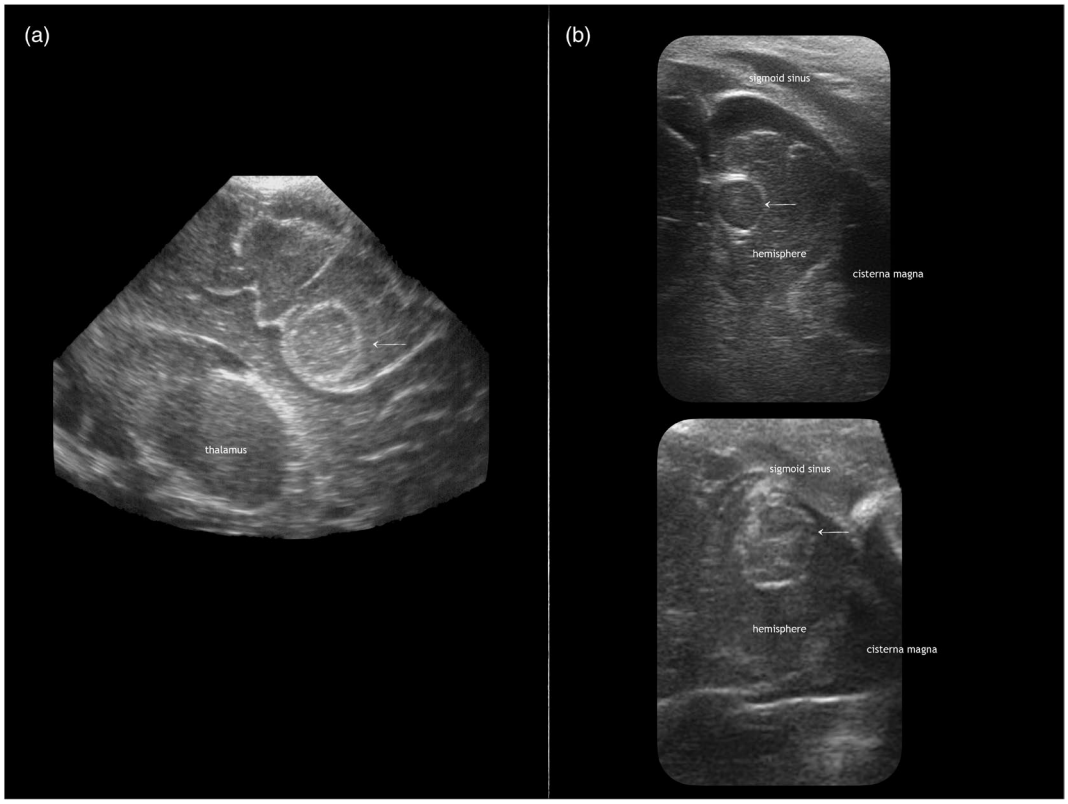

FIGURE 9 *Staphylococcus aureus* abscess. (a) Cerebral abscess in the paracentral lobule with *S. aureus* in a term infant (parasagittal cranial ultrasound image). (b) Cerebellar abscess with *S. aureus* (two different infants born preterm, both with mastoid insonations).

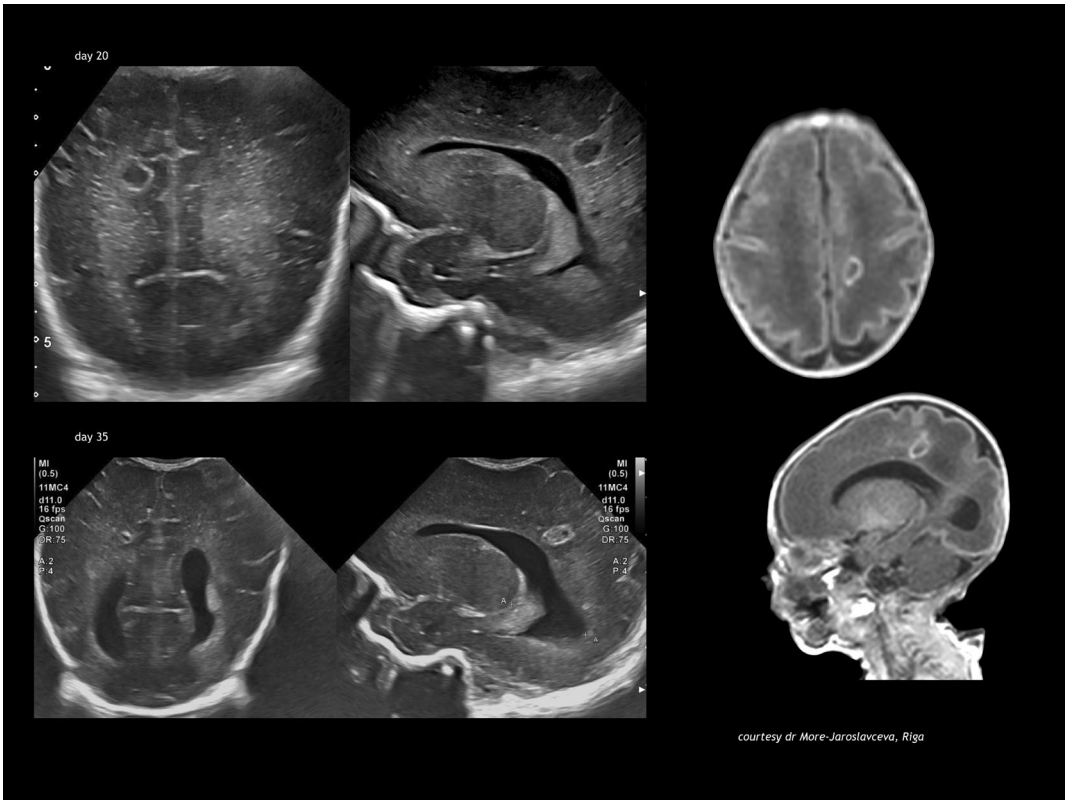

FIGURE 10 *Aspergillus* focal infection. HELLP syndrome, Caesarean section at gestational age 27 weeks, birthweight 600 g, skin infection at peripheral deep line on day 13, *Aspergillus* in blood and cerebrospinal fluid day 14; cranial ultrasound showing cyst in the right frontoparietal region. Magnetic resonance imaging result of 6-week intravenous liposomal amphotericin B followed by voriconazole. Focal post-inflammatory cavity in the right parietal subcortex.

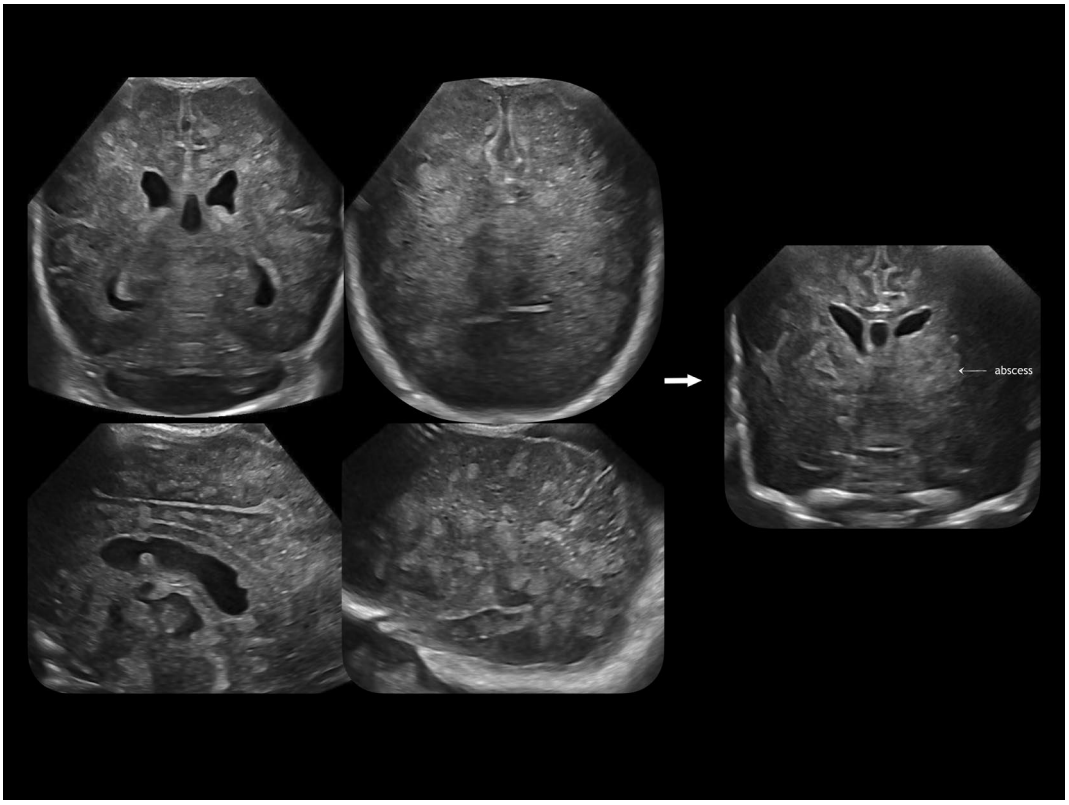

FIGURE 11 *Candida* encephalitis with abscess formation. Infant born preterm (gestational age 29 weeks): acute stage of *C. albicans* encephalitis with disseminated hyperechoic nodules in the parenchyma and on choroid plexus; early macro-abscess formation 1 week later due to confluence of several nodules.

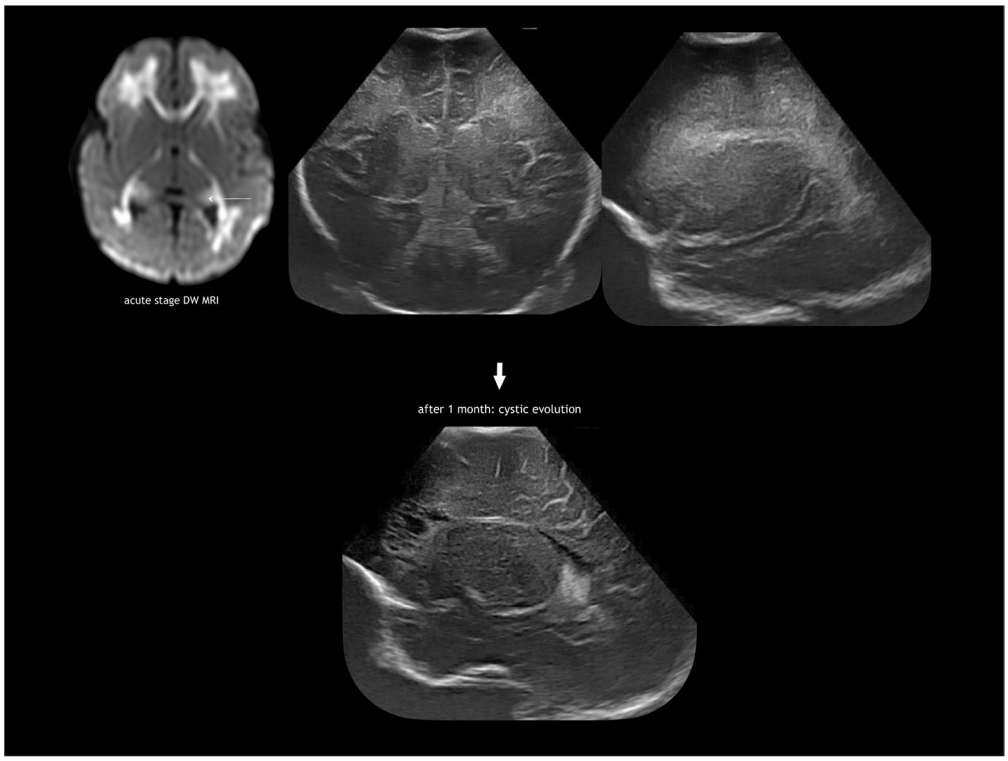

FIGURE 12 Enterovirus encephalitis–meningitis. Infant born late preterm, seizures caused by enterovirus meningitis at 2 weeks; cranial ultrasound images showing early hyperechoic white matter change evolving into cavitation mainly in the frontal lobes. Observe bilaterality and near symmetry. Observe restricted diffusion in the corresponding periventricular areas and network injury in pulvinar on DW MRI in the acute stage (arrow) as well as restricted diffusion in the corpus callosum, optic radiation, and posterior limb of the internal capsule. Abbreviation: DW MRI, diffusion-weighted magnetic resonance imaging.

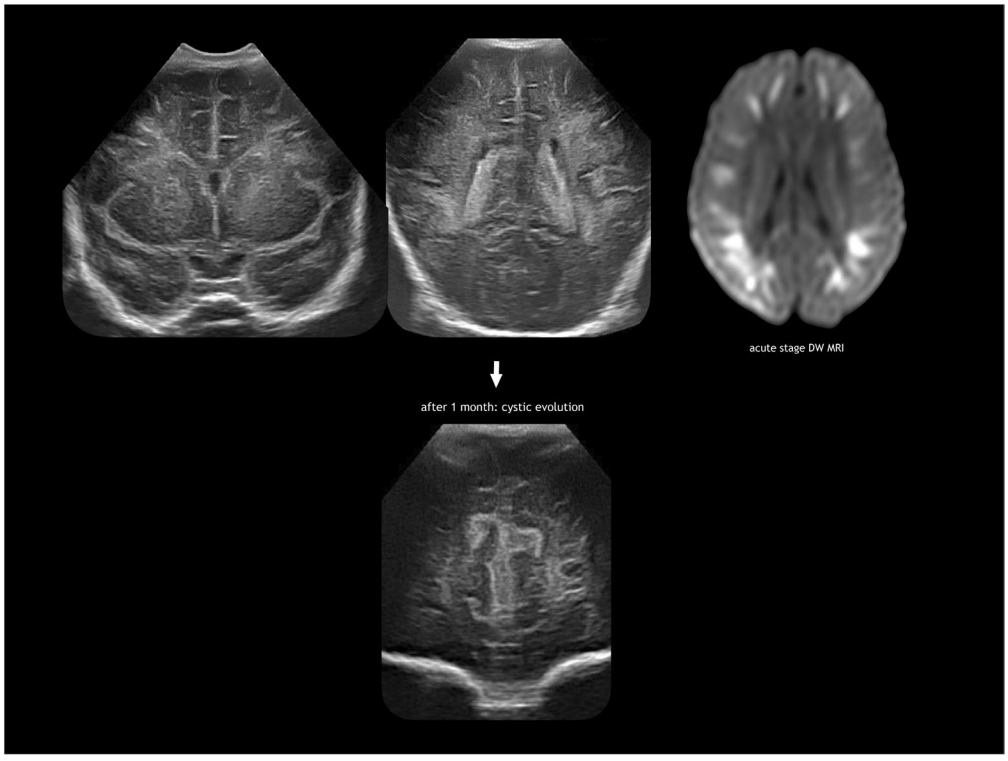

FIGURE 13 Rotavirus encephalitis–meningitis. Infant born late preterm, seizures caused by rotavirus infection at 2 weeks after birth. Cranial ultrasound imaging showing initial hyperechoic change similar to flaring in preterm white matter injury, but ending in cavitation in the frontal areas (below). Right diffusion-weighted magnetic resonance imaging showing the acute changes. Abbreviation: DW MRI, diffusion-weighted magnetic resonance imaging.

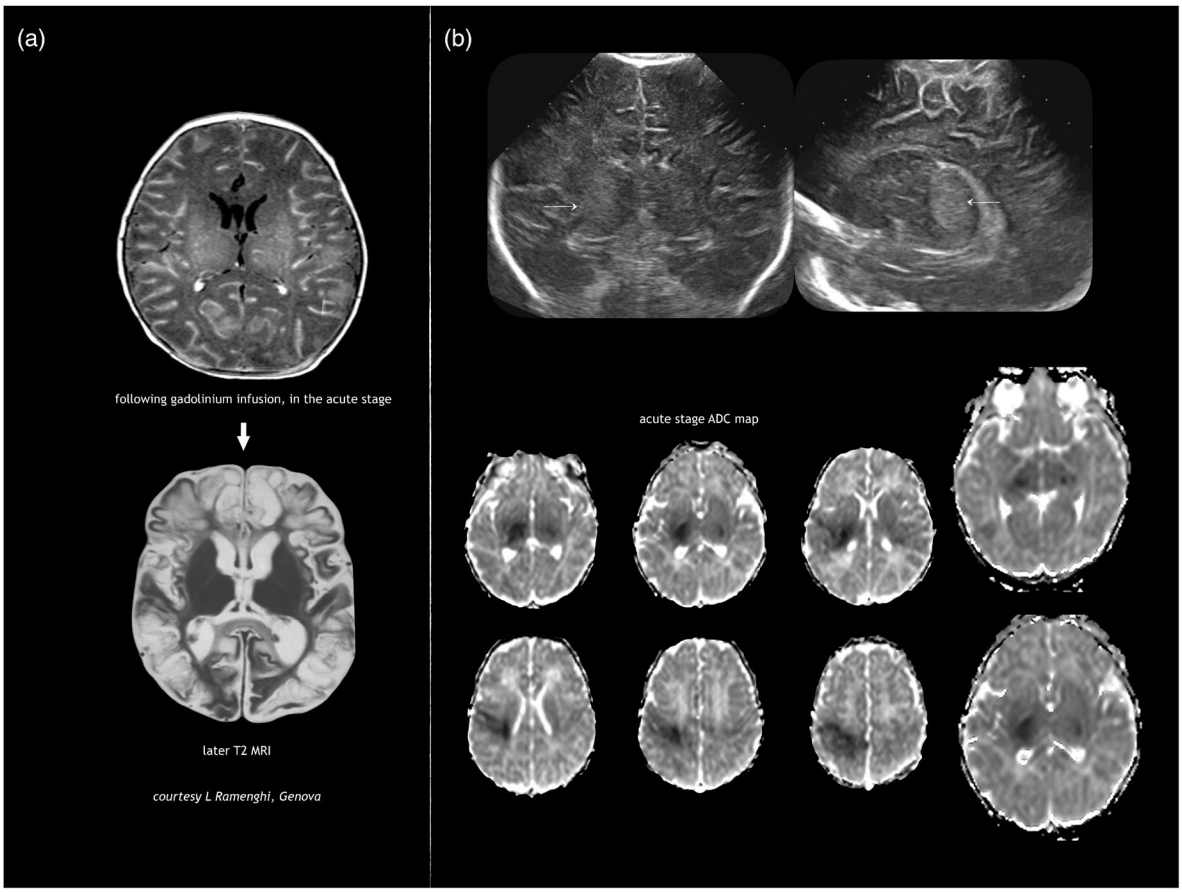

FIGURE 14 Herpes simplex virus encephalitis. (a) Term-born infant with the acute changes and total brain destruction on MRI, caused by HSV (courtesy L Ramenghi, Genova). (b) A term infant, seizures and fever day 28: thalamo-cortical injury pattern of Herpes simplex virus infection; cranial ultrasound shows hyperechoic change in right thalamus, this is confirmed on ADC map MRI. Abbreviation: ADC, apparent diffusion coefficient; MRI, magnetic resonance imaging.

with a broad selection and explanation of high-quality imaging examples of the most important pathogens involved in neonatal CNS infection, will provide the clinician a guide to appropriate diagnosis and a starting point for prompt and adequate treatment, which is crucial to avoid further brain injury and thus to improve outcome.

CONCLUSION

CUS plays an important role in bacterial, fungal, and viral CNS infection. Different causative microorganisms can induce characteristic neuroimaging patterns and CUS is helpful for early recognition. This offers the clinician information for prompt and adequate treatment which is crucial to improve outcome. Moreover, serial scanning also plays an important role in monitoring the evolution of complications such as ventricular dilatation. We recommend at least one MRI scan in every neonate with a meningitis complicated by seizures or an abnormal neurological examination, and in all neonates who have CUS abnormalities, to show the full extent of CNS involvement and help to provide optimal prognostication of outcome.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable - no new data generated.

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