Seminars in Fetal and Neonatal Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Seminars in Fetal and Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Neonatal encephalopathy: Etiologies other than hypoxic-ischemic encephalopathy

A.G. Sandoval Karamian [a], S. Mercimek-Andrews [b], K. Mohammad [c], E.J. Molloy [d,e,f], T. Chang [g,h], V. Chau [i], D.M. Murray [j], C.J. Wusthoff [k,*], on behalf of the Newborn Brain Society Guidelines and Publications Committee [1]

[a] Children's Hospital of Philadelphia, Division of Neurology, 3501 Civic Center Blvd Office 1200.12, Philadelphia, PA, 19104, USA
[b] Biochemical Geneticist, Department of Medical Genetics, University of Alberta, 8-39 Medical Sciences Building, 8613 – 144 Street, Edmonton, T6G 2H7, Alberta, Canada
[c] Cumming School of Medicine, University of Calgary, Alberta Children's Hospital, Room B4-286, 28 Oki drive NW, Calgary, AB, T3B 6A8, Canada
[d] Trinity College, the University of Dublin, Trinity Translational Medicine Institute, Dublin, Ireland
[e] Children's Health Ireland at Tallaght and Crumlin & and Coombe Women's and Infants University Hospital, Dublin, Ireland
[f] Trinity Research in Childhood Centre (TRiCC), Trinity Academic Centre, Tallaght University Hospital, Dublin 24, Ireland
[g] George Washington University School of Medicine & Health Sciences, Washington, DC, 20010, USA
[h] Neonatal Neurology Program, Children's National Hospital, 111 Michigan Ave NW, Washington, DC, 20010, USA
[i] Neurology, Neonatal Neurology Program, The Hospital for Sick Children, 555 University Avenue, Toronto ON, M5G 1X8, Canada
[j] Deptartment of Paediatric and Child Health, University College Cork, ARm 2.32, Paediatric Academic Unit, Floor 2, Seahorse Unit, Cork University Hospital, Wilton, Cork, T12 DCA4, Ireland
[k] Division of Child Neurology, Division of Pediatrics- Neonatal and Developmental Medicine, Stanford Children's Health, 750 Welch Road, Suite 317, Palo Alto, CA, 94304 USA

ARTICLE INFO

Keywords:
Neonatal intensive care
Hypoxia-ischemia
Brain
Neonatal encephalopathy
Brain diseases
Inborn errors of metabolism
Central nervous system
Vascular malformations
Perinatal stroke
Neuromuscular disorders

ABSTRACT

Neonatal encephalopathy (NE) describes the clinical syndrome of a newborn with abnormal brain function that may result from a variety of etiologies. HIE should be distinguished from neonatal encephalopathy due to other causes using data gathered from the history, physical and neurological exam, and further investigations. Identifying the underlying cause of encephalopathy has important treatment implications. This review outlines conditions that cause NE and may be mistaken for HIE, along with their distinguishing clinical features, pathophysiology, investigations, and treatments. NE due to brain malformations, vascular causes, neuromuscular causes, genetic conditions, neurogenetic disorders and inborn errors of metabolism, central nervous system (CNS) and systemic infections, and toxic/metabolic disturbances are discussed.

1. Introduction

Encephalopathy in neonates is broadly defined as brain dysfunction in a newborn manifesting as alteration in mental status and abnormal neurologic examination. Altered mental status (including irritability, decreased responsiveness, lethargy, or stupor), respiratory depression, abnormal tone and/or movements, abnormal reflexes, seizures, and impaired feeding may be present in varying degrees in an encephalopathic neonate [1]. Neonatal encephalopathy (NE) describes a clinical syndrome without attributing a specific cause. NE may result from acute or chronic hypoxic-ischemic injury, brain malformations, vascular injuries (including stroke), inborn errors of metabolism, and other causes. Hypoxic-ischemic encephalopathy (HIE) is a specific diagnosis and applies only when a neonate has

* Corresponding author.
E-mail addresses: sandovalka@email.chop.edu (A.G. Sandoval Karamian), saadet@ualberta.ca (S. Mercimek-Andrews), Khorshid.mohammad@ahs.ca (K. Mohammad), eleanor.molloy@tcd.ie (E.J. Molloy), tchang@childrensnational.org (T. Chang), vann.chau@sickkids.ca (V. Chau), d.murray@ucc.ie (D.M. Murray), wusthoff@stanford.edu (C.J. Wusthoff).
[1] Newborn Brain Society, PO Box 200783, Roxbury Crossing, MA 02120. Email: publications@newbornbrainsociety.org

https://doi.org/10.1016/j.siny.2021.101272

Available online 4 August 2021

encephalopathy that is known or highly suspected to be due to a hypoxic-ischemic event [1–3].

The term birth asphyxia, indicating impaired placental perfusion and gas exchange resulting in hypoxia, ischemia and acidosis, historically was used to describe HIE [2,4]. Current guidelines from the American College of Obstetricians and Gynecologists (ACOG) and endorsed by the American Academy of Pediatrics (AAP) use instead the term HIE, and suggest this specific diagnosis should be reserved for cases with clear evidence of an acute peripartum or intrapartum event [3]. Fetal and neonatal signs consistent with an acute peripartum or intrapartum event include: 1) Apgar scores less than 5 at 5 and 10 min, 2) cord or early neonatal acidemia with pH < 7.0 and/or base deficit ≥12 mmol/L, 3) pattern of brain injury on magnetic resonance imaging or spectroscopy consistent with hypoxia-ischemia, and 4) multisystem organ failure, including renal injury, hepatic injury, hematologic abnormalities, cardiac dysfunction, metabolic derangements and gastrointestinal injury. Additional factors consistent with an acute peripartum or intrapartum event include: 1) the presence of a sentinel event immediately before or during labor and delivery (uterine rupture, placental abruption, umbilical cord prolapse, amniotic fluid embolus with associated severe maternal hypotension and hypoxemia, maternal cardiovascular collapse, fetal exsanguination from fetomaternal hemorrhage, vasa previa, or shoulder dystocia), 2) fetal heart rate abnormalities consistent with an acute peripartum or intrapartum event, and 3) no evidence of other contributing factors such as abnormal fetal growth, maternal infection, neonatal sepsis, or chronic placental lesions [3].

HIE may be distinguished from neonatal encephalopathy due to other causes using the history, physical and neurological exam, and investigations, as summarized in Table 1 [5,6]. Neonatal encephalopathy due to any cause may feature exam findings of depressed level of consciousness, decreased reactivity, decreased spontaneous activity, abnormal tone, poor suck and/or diminished primitive reflexes. An etiology other than HIE should be considered when the exam also reveals congenital anomalies, microcephaly, contractures, spasticity, absent deep tendon reflexes, hepatomegaly, or rash/stigmata of infection [7]. By contrast, isolated hypoglycemia may cause NE in the absence of HIE. Neuroimaging may reveal findings suggestive of a cause other than hypoxic-ischemic injury [6,8,9]. EEG may reveal neonatal seizures in NE due to any cause, but may also provide evidence of early infantile epileptic encephalopathy in some cases. Placental pathology can be helpful in providing evidence of a chronic process such as placental insufficiency, or more acute processes including chorioamnionitis or placental abruption [5].

Table 1
Features distinguishing HIE from other causes of NE.

	Suggestive of HIE	Suggestive of other NE
History	- Sentinel event during labor or immediately before/during birth - Fetal heart rate abnormalities consistent with an acute event - Need for resuscitation at birth - Apgar <5 at 5 and 10 min - Encephalopathy evident immediately from birth	- IUGR - Oligohydramnios or polyhydramnios - Maternal infection - Maternal medication or substance use - Family history of genetic disorders, neonatal illness, or seizures - Delayed onset of symptoms after birth
Exam	- Abnormal Sarnat exam in isolation	Abnormal Sarnat exam in association with: - Congenital anomalies - Microcephaly - Macrocephaly - Contractures - Spasticity - Absent deep tendon reflexes - Hepatosplenomegaly - Rashes/stigmata of infection
Labs	- Cord pH or blood gas with acidosis (pH < 7.0) - Elevated lactate - Evidence of multisystem end-organ dysfunction (abnormal CK, BUN/Cr, LFTs)	- Electrolyte derangements (hypoglycemia, hypermagnesemia) - Elevated WBC count, inflammatory markers - Positive urine or meconium toxicology screens - Hyperammonemia, hypouricemia
Imaging	- HUS or MRI showing pattern of brain injury consistent with HIE	- HUS or MRI with evidence of chronic injury (e.g., cystic changes, atrophy) soon after birth - HUS or MRI with other brain abnormality or injury (brain malformations, stroke, hemorrhage, meningitis/encephalitis)
Other studies	- Acute/subacute placental lesions on placental pathology, with or without chronic changes	- Chronic placental lesions on placental pathology

It is important to note that encephalopathy can be acute or chronic. Subacute or remote in utero events may cause chronic encephalopathy that is recognized after birth. It may be difficult to distinguish whether encephalopathy is chronic or acute in the hours after delivery; subsequent evolution of the condition is often informative.

Furthermore, it is helpful to distinguish that meeting eligibility criteria for therapeutic hypothermia is not the same as confirming a diagnosis of HIE. Therapeutic hypothermia is the standard of care for suspected HIE; eligibility criteria for hypothermia are intentionally broad to include any neonate who *might* benefit, as the benefits of cooling for potential HIE outweigh the risks of treating a neonate who is subsequently discovered a different etiology for NE [10]. Thus, eligibility for or receipt of therapeutic hypothermia in the neonatal period does not confirm a diagnosis of HIE. Therapeutic hypothermia is recommended for all neonates with encephalopathy who meet institutional eligibility criteria, even when the cause of NE is unknown in the first hours after birth.

This review focuses on causes of NE that could potentially be confused for HIE. It does not include those conditions which cause encephalopathy, but have a presentation clearly distinct from that of HIE in a newborn. We summarized numerous causes as well as key features and investigations in Fig. 1.

1.1. Vascular conditions

Vascular malformations and injuries can present with acute findings similar to HIE, with potential distinguishing features outlined in Table 2. Differentiating cerebral vascular lesions from HIE is important as they may require immediate interventions other than therapeutic hypothermia and may warrant further investigation for underlying risk factors [11,12].

The most common vascular injury mimicking HIE is arterial ischemic stroke (AIS); this diagnosis shares some overlapping risk factors and delivery room presentations with HIE [13,14]. Neonatal AIS and HIE can coexist in 4–6% of cases [15,16]. Unlike HIE, however, infants with AIS are less likely to have fetal heart tracing abnormalities, sentinel events, or perinatal acidosis. Other non-specific features, such as failure to progress or prolonged labor, may be seen in both. AIS presents most frequently in neonates not as immediate, severe encephalopathy, but rather as focal seizures several hours after birth, typically in the first or second day of life. Seizures may be apparent as mostly unilateral clonic motor jerks, but also may manifest as unexplained apnea in the setting of lethargy or mild encephalopathy. In AIS, EEG typically demonstrates asymmetry [15,17,18]. Management of AIS focuses on acute seizure control and later rehabilitation.

Cerebral sinus venous thrombosis (CSVT) leading to hemorrhagic infarct and/or intraventricular hemorrhage (IVH) is another abnormality that can mimic HIE or occur in critically ill neonates with NE of any cause, typically with later onset of symptoms [19]. Infants with NE who present with refractory seizures, coagulopathy, or persistent

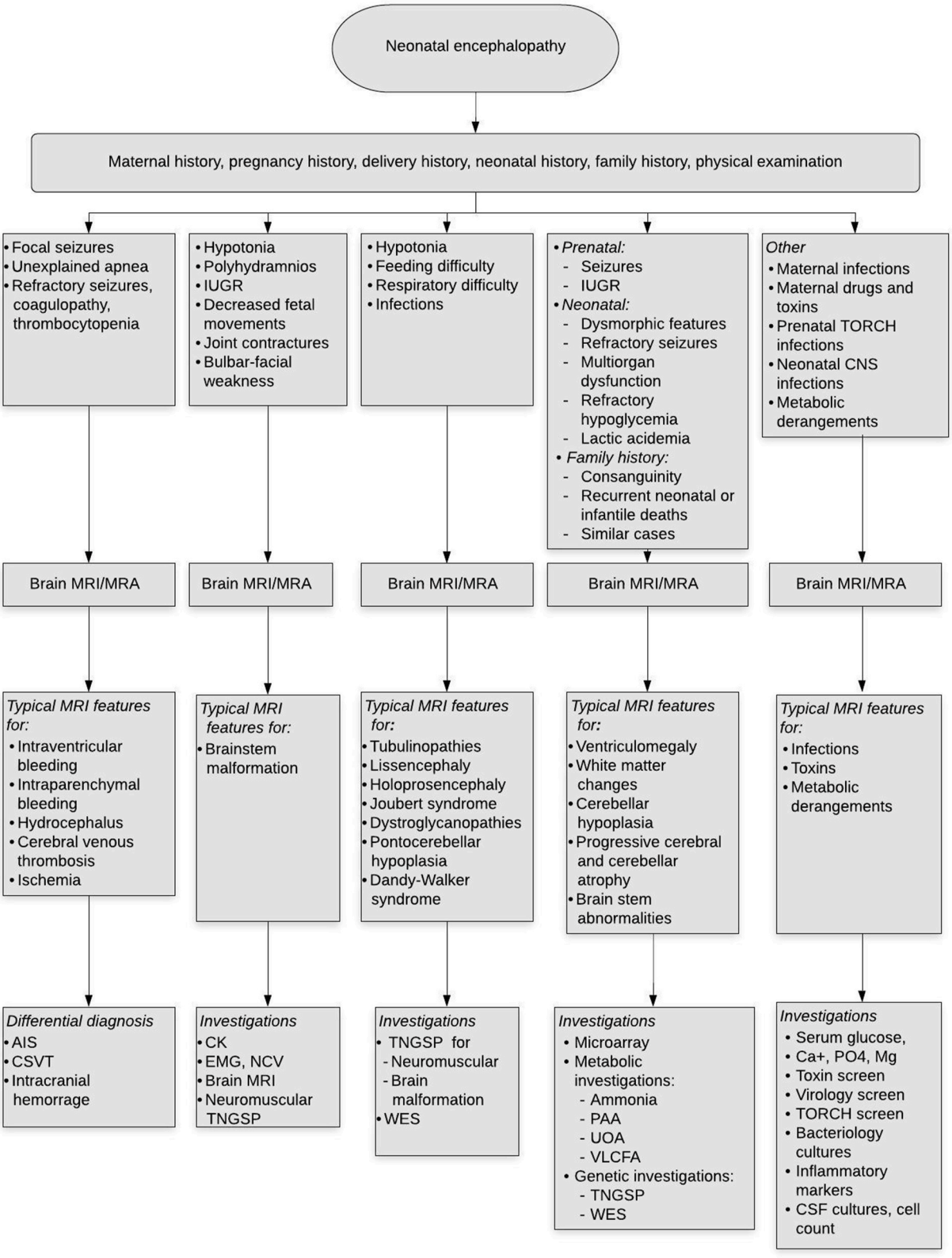

Fig. 1. Approach to the evaluation of the encephalopathic neonate, with key etiologies, clinical features, and investigations.

unexplained thrombocytopenia should be investigated for possible CSVT. Additional risk factors for CSVT include sepsis/infection and dehydration. MR venography is helpful to evaluate for CSVT [20]. Early transcranial color doppler ultrasonography is a reasonable bedside alternative in unstable infants to help evaluate for thrombosis in the major cerebral sinuses [21,22]. These diagnoses have unique treatment implications, as CSVT may require treatment with anticoagulation in the acute phase when there are no contraindications and there is ongoing risk of thrombosis or progression of the CSVT [23]. IVH may require monitoring for post hemorrhagic hydrocephalus.

Table 2
Vascular causes of encephalopathy, compared to HIE.

	Perinatal risk factors	Encephalopathy	Associated hemodynamic instability	Seizures/EEG background	Brain imaging	Management
HIE	Common	Common within 6 h of birth	Common due to poor cardiac contractility and/or decreased vascular tone	Seizures can start any time in the first 24 h after birth. EEG background with symmetric discontinuity and or suppression	HIE brain injury patterns on MRI (bilateral watershed, white matter, or deep gray matter injury)	TH, Seizure management, and multisystem support
Arterial Ischemic Stroke	Uncommon	Uncommon within 6 h of birth	Uncommon	Commonly seizures start 1–2 days after birth. EEG may show asymmetry with normal EEG background in the non-affected area	Focal ischemia in an arterial distribution	Seizure control
Cerebral sinovenous thrombosis (CVST)	Uncommon	Common if symptomatic	Uncommon	Seizures can occur. EEG background can be normal, show excess vertex sharps, or may show asymmetric background	May show IVH and/or intraparenchymal hemorrhage, hydrocephalus, thrombosis on MR venogram	Seizure control, may require heparin therapy
Cerebral vascular malformation	Uncommon	If rupture/ hemorrhage occurs	Uncommon, except for vein of Galen malformation	May present with seizures when close to the cortex or complicated with hemorrhage	MRI shows the vascular malformation. Cranial ultrasound doppler is helpful to show flow turbulence through the malformation	May require surgical or IR intervention
Subgaleal Hemorrhage	Common	Uncommon in early stages	May present with hypovolemic shock	EEG amplitudes can be suppressed due to scalp edema and subgaleal hemorrhage at electrodes, with normal continuity of EEG background	Usually no lesion unless secondary to hypovolemia	Cardiovascular resuscitation: volume replacement with normal saline, FFP, and blood transfusion

Abbreviations: HIE = Hypoxic Ischemic Encephalopathy, EEG = electroencephalogram, MRI = magnetic resonance imaging, IR = interventional radiology, TH = therapeutic hypothermia, IVH = intraventricular hemorrhage, FFP = fresh frozen plasma.

Hemorrhage may also develop in the absence of CSVT. Intracranial hemorrhages may result from specific genetic mutations (apoptosis-inducing factor mitochondrion-associated 1 (*AIFM1)* [24], collagen type IV alpha 1 and 2 chain (*COL4A1* and *COL4A2)*[25,26]) or vascular malformations such as a vein of Galen malformation [27], arteriovenous malformation in neonates with hereditary hemorrhagic telangiectasia [28], or pial arteriovenous fistulae [29]. Some congenital syndromes such as Sturge-Weber syndrome may present with encephalopathy, intracranial hemorrhages, or refractory seizures, though imaging indicates the etiology in these cases [11,30].

Subgaleal hemorrhage is a life-threatening emergency which may require immediate intervention with fluid resuscitation and blood products [31]. Infants with a history of traumatic birth or vacuum/forceps-assisted delivery should be checked and monitored closely for the presence and/or progression of subgaleal hemorrhage [12].

1.2. Neuromuscular disorders

Because much of the neonatal neurologic exam relies on tone and general movements, neuromuscular conditions presenting with hypotonia at or immediately after birth can be initially mistaken for HIE [3]. The characteristic signs of HIE, i.e., depressed mental status, hypotonia, abnormal posture, decreased or absent primitive reflexes, and apnea, are also common in many neonatal neuromuscular conditions. History and exam may indicate a neuromuscular disorder. Polyhydramnios (suggesting abnormal fetal suck and swallow), poor fetal growth, reduced or absent fetal movements, and/or joint contractures are clinical features often seen with congenital neuromuscular disorders rather than HIE [32]. Accurate assessment of encephalopathy, weakness, and tone in a newborn is difficult: at this age, movements are predominantly defined by brainstem and spinal cord reflexes and do not indicate full alertness or awareness. Conversely, the absence of movement does not necessarily indicate reduced consciousness, as in conditions where profound weakness prevents motor response. Clinical findings such as poor suck and/or swallow are non-specific and should be assessed in context of the overall exam. Muscle tone is most comprehensively assessed in active-awake, quiet-awake and sleep states, and should be placed in the context of the newborn's gestational age. Typically, weakness in HIE is diffuse and symmetric, while facial or bulbar weakness related to dysfunction of the lower cranial nerves out of proportion to appendicular weakness is more suggestive of a neuromuscular etiology. For example, facial sparing weakness is typical of congenital spinal muscular atrophy; prominent facial-bulbar weakness and/or ophthalmoparesis may be seen with congenital myopathies or myasthenic syndromes [33]. Distal hypotonia or weakness out of proportion to the degree of encephalopathy on exam is suggestive of neuromuscular disorders. A common pitfall is that ptosis, prominent in Prader Willi, congenital myasthenic syndromes, and congenital myopathies, can give the appearance of encephalopathy because the eyes remain closed despite stimulation. Presence of reduced muscle bulk, spasticity, or joint contractures/arthrogryposis typically suggest a peripheral nervous system condition and are not signs of an acute peripartum or intrapartum event. Deep tendon reflexes are usually decreased or absent with neuromuscular disorders, but also typically reduced immediately following acute brain injury before transitioning to hyperreflexia. Reduced or lack of spontaneous movements are non-specific as this can be associated with severity of encephalopathy rather than a neuromotor finding.

Congenital muscular dystrophies with associated brain malformations can present with mild to moderate encephalopathy in the neonatal period. Mild dysmorphic facial features including myopathic facies (elongated face, dolichocephaly, ptosis, tented mouth, high-arched palate) may be present in neuromuscular disorders. A hypophonic cry or tongue fasciculations can be seen with congenital myopathies or spinal muscular atrophy, respectively. Percussion myotonia, which is myotonia elicited by percussion of the thenar eminence or finger extensor muscles, may or may not be present in neonates with myotonic dystrophy, but is more easily elicited on exam of the mother [34,35]. Fluctuating weakness or fatigability may indicate a congenital myasthenic syndrome.

Serum studies, nerve conduction studies (NCS) and electromyography (EMG), muscle ultrasound, muscle biopsy, brain MRI and genetic

testing can be useful tools to establish a precise neuromuscular diagnosis [32]. Selecting and prioritizing additional studies should be done in consultation with a pediatric neurologist or neuromuscular specialist. Elevated creatine kinase (CK) levels are seen with muscular dystrophies but are often normal or minimally elevated in congenital myopathies. A normal neonatal CK does not exclude a neuromuscular disorder, and CK may be elevated with HIE, especially in the first days of life. Brain MRI may be normal in neuromuscular conditions, or with mild non-specific findings. Absence of acute brain injury is typical. Some congenital muscular dystrophies include both muscle involvement and CNS malformations, such as dystroglycanopathies. Similarly, merosin deficiency may be accompanied by diffuse white matter abnormalities [36]. EMG/NCS can help localize symptoms to the nerve, muscle or neuromuscular junction and are ideal for immune myopathies and congenital myasthenic syndromes. Muscle biopsies are less common as they are replaced with more rapid genetic testing, but are still useful in the diagnosis of immune myopathies, dystrophies (characterized by prominent degeneration-regeneration or fibrous fatty replacement), and congenital myopathy (characterized by small muscle fibers with central nuclei, nemaline rods, central cores or fiber type disproportions) [33]. Muscle ultrasound or MR imaging may provide enough information to direct genetic testing and potentially avoid muscle biopsy.

In some countries, newborn screens may now test for Pompe, spinal muscular atrophy, or Duchenne muscular dystrophy given the availability of enzyme and/or genetic therapies which require prompt initiation to maximize functional outcome [37]. The importance of rapid precise genetic diagnosis of newborns with neuromuscular disorders is rising as targeted enzyme treatments, gene therapies, and clinical trials become available. Of note, gene panels or whole exome/genome sequences will not identify all neuromuscular disorders. Nucleotide repeat disorders, such as myotonic dystrophy type 1, require specific testing, such as PCR or Southern blot, for identification.

1.3. Central nervous system malformations

Malformations of the CNS are an uncommon cause of neonatal encephalopathy. Severe malformations of the brain are often diagnosed prenatally on ultrasound; yet it remains possible for the first suspicion to arise after birth. The cardinal clinical features include neonatal hypotonia, which may cause feeding or respiratory difficulties. With the exceptions of congenital muscular dystrophies, CNS features dominate the clinical presentation.

Tubulinopathies comprise a wide range of brain malformations caused by mutation of one of seven genes encoding different isotypes of tubulin. One of the pathognomonic MRI features is an unusual orientation of the basal ganglia, found in 75 % of cases [38,39]. It is suspected to result from abnormal axon guidance of the corticospinal tract through the internal capsule, leading the head of the caudate to protrude into the ventral horn of the ventricles (“hooked aspect” of the anterior horn). Other associated anomalies include partial or complete agenesis of the corpus callosum (40 %) and cortical dysgenesis (>60 %), such as lissencephaly, microlissencephaly or generalized polymicrogyria-like cortical dysplasia.

Lissencephaly (or agyria) is a congenital disorder of cortical development wherein cerebral convolutions are absent, giving a smooth appearance to the cortex. Affected children with classic lissencephaly have profound developmental and cognitive delays, early and persisting hypotonia, opisthotonus, poor feeding, and seizures [40]. Lissencephaly can be associated with several genetic disorders; one of the most common is Miller-Dieker syndrome, recognized clinically by its distinctive dysmorphic features. In Miller-Dieker syndrome, lissencephaly is always severe [41].

Holoprosencephaly is a malformation characterized by abnormal separation of the cerebral hemispheres or lobes, ranging from “alobar” to “lobar” forms, with “semi-lobar” an intermediate form [42]. In lobar or semi-lobar (incomplete) holoprosencephaly, the hemispheres are variably separated. As a result, the falx cerebri appears hypoplastic and the interhemispheric fissure is incomplete in frontal and occipital regions. Similarly, structures of the posterior fossa are variably developed. Midline craniofacial anomalies, such as hypotelorism or (less frequently) hypertelorism, nasal abnormalities (e.g., single nostril, choanal atresia, or arrhinia), thin lip with indistinct philtrum, cleft lip and/or palate, or micrognathia, can be seen. Most holoprosencephalic infants are hypotonic; spastic diplegia becomes evident later in life. Epilepsy and cognitive impairments are variable [43].

Joubert syndrome and related disorders are a group of ciliopathies sharing the “molar tooth sign”, which results from hypo-dysplasia of the cerebellar vermis, abnormally deep interpeduncular fossa at the level of the isthmus and upper pons, and horizontalized, thickened and elongated superior cerebellar peduncles [44,45]. Joubert syndrome and related disorders are clinically heterogeneous with variable multiorgan involvement (mainly the retina, kidneys, liver and skeleton). The most characteristic neonatal neurological features are hypotonia, often associated with altered respiratory pattern in the neonatal period [46].

The *dystroglycanopathies* are a heterogeneous group of autosomal recessive disorders characterized by hypoglycosylation of alpha-dystroglycan. The phenotype varies. Three conditions are known to be associated with congenital brain malformations, in addition to congenital muscular dystrophy. *Walker-Warburg syndrome* is the most severe form. Brain abnormalities include complete severe cobblestone lissencephaly (type 2), marked hydrocephalus, dysplastic cerebellum, kinking of the brainstem at the pontomesencephalic junction, and complete or partial callosal dysgenesis. Eye abnormalities include congenital cataracts, microphthalmia, and buphthalmos. Motor development is minimal or absent, and death before 1 year of age is usual [47]. *Muscle-eye-brain disease* was originally reported in the Finnish population. Affected neonates present with hypotonia and poor visual alertness. On MRI, pachygyria and polymicrogyria can be seen. Other anomalies include cerebellar and brain stem abnormalities. Structural eye abnormalities may include congenital glaucoma, progressive myopia, retinal atrophy, and juvenile cataracts [47]. *Fukuyama congenital muscular dystrophy* is mainly seen in Japan, due to the presence of a *FKTN* founder mutation. Structural brain involvement includes cobblestone lissencephaly, white matter abnormalities, midbrain hypoplasia, and cerebellar abnormalities. Clinically, affected patients show a combination of generalized muscle weakness, severe brain involvement with cognitive impairment, frequent seizures, and abnormal eye function (e.g., poor visual pursuit, strabismus, myopia/-hyperopia, cataracts) [48]. Pseudohypertrophy of the tongue, calves, and quadriceps muscles can be seen [49].

Dandy-Walker syndrome, consisting of hypoplasia, elevation, and rotation of the cerebellar vermis and cyst like dilatation of the fourth ventricle, with variable degree of posterior fossa enlargement and hydrocephalus, is a rare cause of neonatal encephalopathy; most neonates are asymptomatic or mildly symptomatic at birth [50,51].

1.4. Genetic disorders

Next generation sequencing technologies have identified several genetic etiologies of neonatal encephalopathy, including a group of genetic disorders that mimic the clinical and neuroimaging features of HIE [52]. In studies undertaken to identify genetic disorders in neonatal encephalopathy, the diagnostic yield of whole exome sequencing (WES) or whole-genome sequencing (WGS) was between 10 and 40 % [53–56]. Detailed investigations identified underlying genetic etiologies in a limited number of patients and can confirm a diagnosis of cytochrome oxidase deficiency [57], pyridoxine-dependent epilepsy [58], molybdenum cofactor deficiency [59], glycogen storage disease type IV [60], and X-linked centronuclear myopathy [61]. It is important to include genetic and inherited metabolic disorders in the differential diagnosis of neonatal encephalopathy, particularly to guide treatment and counsel families regarding prognosis and recurrence risks.

There are several important signs and symptoms to suggest the possibility of underlying genetic disorders in neonates with encephalopathy. Prenatal history of oligohydramnios, polyhydramnios, decreased fetal movements, increased fetal movements or hiccups, brain malformations and/or anatomical defects in prenatal ultrasounds and fetal MRI can suggest underlying genetic disorders. Genetic disorders should be considered in encephalopathic neonates with dysmorphic features, refractory seizures, respiratory insufficiency, multiorgan dysfunction, severe hypoglycemia, hyperammonemia, or metabolic acidosis with elevated anion gap and lactic acidemia. A family history of consanguinity of parents, recurrent pregnancy losses, recurrent neonatal or infantile deaths, developmental delay, cognitive dysfunction, epilepsy, or congenital malformations may also suggest underlying genetic disorders.

Genetic disorders presenting with neonatal encephalopathy are summarized in Table 3 [62], including broad categories of genetic syndromes, neonatal onset neurodegenerative disorders, genetic epileptic encephalopathies and inherited metabolic disorders for their clinical and neuroimaging features. Suggested investigations for the diagnosis of inherited metabolic disorders are listed in Table 3. In neonates with dysmorphic features, karyotype and/or chromosomal microarray should be chosen as the first-line genetic investigation. In infants with neonatal seizures, neuromuscular findings, or MRI features which are not typical for HIE, targeted next generation sequencing panels or WES should be applied if basic metabolic investigations do not identify a treatable inherited metabolic disease. Despite extensive investigations, an underlying genetic diagnosis is not confirmed in about two-third of the patients with neonatal encephalopathy.

It is important to consider treatable inherited metabolic disorders in the differential diagnosis of neonatal encephalopathy. The confirmation of the diagnosis allows appropriate and early treatment to prevent severe neurodevelopmental consequences.

1.5. Central nervous system infections

Systemic infection, inflammation, and particularly CNS infection can co-exist with HIE, or may cause neonatal encephalopathy without accompanying HIE. Infections represent an important cause of NE due to the potential immediate treatment implications, therefore a complete sepsis evaluation is imperative in neonates presenting with encephalopathy. The decision to perform a lumbar puncture should be made on a case by case basis based on the level of clinical suspicion for meningitis/encephalitis, taking into account the patient's clinical presentation, and individual and regional risk factors for CNS infection. In many cases, antibiotics are initiated in neonates with encephalopathy prior to an opportunity for lumbar puncture, which may necessitate a course of empiric treatment if subsequent evaluation raises a question of CNS infection. Interpretation of the sepsis evaluation in neonates undergoing therapeutic hypothermia must be cautious, as cooling delays the rise in CRP and may cause decreased leukocyte and neutrophil counts [63]. Broad spectrum antibiotics are often commenced until inflammatory markers and blood cultures are available. In addition, viral PCR and further investigations may be required depending on other features such as known maternal herpes simplex virus (HSV) infection, or associated microcephaly and intracranial calcifications. In a study from Uganda, multiplex real-time PCR assays for pathogens (gram positive and gram negative bacteria, CMV, herpes simplex virus (HSV) and P. falciparum) were performed on whole blood taken from 202 encephalopathic and 101 control infants. Culture alone yielded 3.6 %, increasing to 8.95 % with PCR in combination; more infants with NE had pathogenic bacteria than controls [64].

Infection has been commonly described in the etiology of NE and administration of endotoxin in animal models of neonatal HIE has been shown to sensitize the brain to increased hypoxic-ischemic injury [65–68]. The combination of infection and HIE has also been associated with increased cerebral palsy (CP) in children [69]. Neonates who developed CP in the context of maternal infection were more likely to have a history of NE, a requirement for inotropic support, seizures without meningitis, need for intubation and lower Apgar score at 5 min compared to CP without maternal infection [69]. Increased inflammatory cytokines such as IL-6 and IL-8 are associated with abnormal neuroimaging in infants with NE [70]. There is also a strong association between chorioamnionitis, NE, and CP in the term infant [71,72]. Clinical, imaging, and laboratory features of specific diagnoses are included in Table 4.

Group B *Streptococcal* (GBS) infection was associated with NE in 0.58 % of cases and there was a higher mortality when GBS and NE were combined [73]. Parker et al. found that infants with NE had chorioamnionitis in 40 % and in 11 % also had a sentinel event [74]. In 24 % of cases of NE on the Vermont Oxford network, there also was an associated antenatal inflammatory issue [75]. A comparison of neonates with GBS and *E. coli* meningitis found similar CSF lab values, but on neuroimaging, infarcts were more frequent with GBS, while hydrocephalus was more common with *E. coli* [76]. The hydrocephalus following infection can occur in the absence IVH, primarily related to damage to the arachnoid granulations and impaired CSF reabsorption. Falck et al. showed that the neuroprotective effect of therapeutic hypothermia in an animal model was dependent on the pathogen and was more protective in gram-positive versus gram-negative infections [77]. Similarly, it was questioned if therapeutic hypothermia was less efficient in neonates with HIE in the context of chorioamnionitis [78].

Congenital syphilis can present with intracranial hematoma and disseminated intravascular coagulation, although this is very rare and usually would not present with encephalopathy [79]. The stigmata of congenital syphilis are not always obvious and serological testing is required. *Listeria monocytogenes* can present with symptoms of central nervous disease in the newborn [80]. A recent report from the United Kingdom surveillance network (neonIN) has a case fatality rate of 21 % and an incidence of 3.4 per 100,000 live births [81]. Lee et al. reviewed outcomes following ECMO for neonatal listeriosis and found 86 % survival [82].

TORCH infections are associated with white matter injury and, although linked with neonatal seizures, microcephaly, and intrauterine issues, they do not commonly present as neonatal encephalopathy [83]. In a small NE cohort, clinical and blood culture positive sepsis was detected, but PCR results for neurotrophic viruses were negative [79]. HSV can present with early-onset seizures, more common after the first few days of life. Herpes infection is usually asymptomatic in the mother, but ascending infection is possible after prolonged rupture of membranes. CNS disease occurs in half of the infected neonates. Symptoms typically occur at the end of the second week, including irritability, feeding difficulties, lethargy, seizures and sometimes coma. The diagnosis requires HSV DNA detected by PCR from CSF, but testing may need to be repeated as it is not detected in 30 % of cases in the early stages; and conjunctivae, nasopharynx, anus and suspected vesicles should all be swabbed. On MRI, there are three main patterns of injury associated with HSV including watershed distribution, which is a similar pattern to the injury seen after moderate prolonged hypoxia in term HIE, frontal/temporal lobes, or corticospinal tracts [84]. A three week course of intravenous acyclovir is used for HSV encephalitis with repeat lumbar puncture at 21 days to ensure clearance [85]. Renal function monitoring and adequate hydration are important to prevent nephrotoxicity associated with acyclovir [86].

Severe anemia and fetal hydrops can result from infection in pregnancy with parvovirus and potentially present as NE. Anti-nonstructural protein 1 (NS1) antibodies suggests a recent infection (Qin J et al., 2017). Neuroimaging may reveal cortical dysplasia, heterotopia, hydrocephalus, calcifications, or cerebellar hemorrhage [87]. Although parechovirus, enterovirus, rotavirus, and Chikungunya virus are usually postnatally acquired, the latter can present immediately following birth. Chikungunya virus is mosquito-borne and signs of infection can occur immediately during or after birth, although it typically evolves over

Table 3
Neurogenetic and inherited metabolic disorders presenting with neonatal encephalopathy are summarized for disease category, genetic defect and clinical features.

Category of genetic conditions	Disease	Clinical features	Neuroimaging or EEG features	Genetic Investigations and Findings
Syndromes	Prader-Willi syndrome	Hypotonia, dysmorphic features (bitemporal narrowing, almond-shaped eyes, strabismus, upslanting palpebral fissures, thin upper lip, small mouth, down-turned corners of mouth, hypoventilation, genital abnormalities, small hands and feet, syndactyly), breech presentation, decreased fetal movements, weak cry	Ventriculomegaly, decreased volume of the parietal-occipital lobe, sylvian fissure polymicrogyria, and incomplete insular closure	Microarray deletion or maternal uniparental disomy of 15q11.2-q12
	Congenital central hypoventilation syndrome	Hypoventilation (described as monotonous respiratory rates and shallow breathing in sleep or awake), autonomic nervous system dysregulation, in some newborns neural crest tumors or Hirschsprung disease	Multiple white matter abnormalities, hypothalamus, posterior thalamus, midbrain, caudal raphe, locus coeruleus, lateral medulla, parabrachial pons, cerebellum, insular and cingulate cortex changes	Sanger sequencing and deletion/duplication analysis of *PHOX2B* or multigene panel or WES
	Aicardi-Goutières syndrome	Intrauterine growth retardation, neonatal seizures, jitteriness, poor feeding, hepatosplenomegaly, thrombocytopenia, anemia (resembles congenital infections)	Frontotemporal white matter changes, increased T2 signal intensity around ventricular horns, basal ganglia calcification (on ultrasound and CT)	Multigene panel or WES of *ADAR* *RNASEH2A* *RNASEH2B* *RNASEH2C* *SAMHD1* *TREX1*
Neonatal onset pontocerebellar hypoplasia (PCH)	PCH type 1	Muscle weakness, hypotonia, respiratory insufficiency, congenital contractures	Cerebellum hypoplasia, corpus callosum hypoplasia, cortical atrophy, immature myelination	Multigene panel or WES of *VRK1* *EXOSC3* *EXOSC8* *SLC25A46*
	PCH type 2, 4, 5	Generalized clonus, suck and swallowing incoordination, congenital contractures, polyhydramnios,	Supratentorial atrophy homozygous p. A307S variant 'dragonfly' configuration of cerebellum severely affected hemispheres and relative sparing of the vermis	Sanger sequencing of *TSEN54* or multigene panel or WES
	PCH type 6	Hypotonia, seizures,	Progressive cerebral, pons, cerebellum atrophy	Sanger sequencing of *RARS2* or multigene panel or WES
	PCH type 9	Neonatal clonus, brisk deep tendon reflexes and truncal hypotonia	Pontocerebellar hypoplasia, corpus callosum hypoplasia, characteristic 'Fig. 8' shape of the mesencephalon with hypoplastic cerebral peduncles, ventricular dilatation	Sanger sequencing of *AMPD2* or multigene panel or WES
Genetic neonatal epileptic encephalopathies	*KCNQ2* disease	Asymmetric tonic seizures, apnea, hypotonia	Multifocal epileptiform abnormalities with random attenuation or burst suppression on EEG	Sanger sequencing of *KCNQ2* or multigene panel or WES
	KCNT1 disease	Focal seizures with unilateral motor onset, alternating from one side to other side, lateral deviation of head and eyes, limb myoclonic jerks, increased tone, apnea	Diffuse slowing, abnormal with lack of organization, frequent seizures with shifting laterality on EEG	Sanger sequencing of *KCNT1* or multigene panel or WES
	SCN2A disease	Clustering focal tonic, focal clonic seizures, apnea, hypotonia	Burst-suppression pattern or multifocal spikes on EEG	Sanger sequencing of *SCN2A* or multigene panel or WES
	BRAT1 disease	Diffuse hypertonia, microcephaly, multifocal myoclonic jerk, apnea, bradycardia	Normal initial EEG	Sanger sequencing of *BRAT1* or multigene panel or WES
	GNAO1 disease	Focal seizures	Burst-suppression pattern or multifocal sharp waves in EEG	Sanger sequencing of *GNAO1* or multigene panel or WES
	STXBP1 disease	Hypotonia, epileptic spasms, refractory focal seizures	Burst-suppression pattern, sometimes multifocal abnormalities	Sanger sequencing of *STXBP1* or multigene panel or WES
	SLC13A5 disease	Refractory epilepsy	Normal initial EEG Multiple punctate white matter lesions with diffusion restriction on early MRI	Sanger sequencing of *SLC13A5* or multigene panel or WES
Inherited metabolic disorders	Nonketotic hyperglycinemia	Myoclonic jerks, hiccups, hypotonia, lethargy, apnea, seizures, coma	Posterior limb of the internal capsule, anterior brain stem, posterior tegmental tracts, and cerebellum diffusion restriction on MRI Dysplastic corpus callosum Glycine peak on MRS Burst suppression on EEG	Sanger sequencing of *GLDC* *AMT* *GCSH* or multigene panel or WES
	Sulfite oxidase deficiency	Neonatal refractory seizures, feeding difficulties, rapidly progressive encephalopathy	Loss of gray-white matter differentiation, cerebral edema, progression to cystic encephalomalacia on MRI Low-amplitude, disorganized background, multifocal epileptiform discharges, burst suppression on EEG	Urine s-sulfocysteine (elevated) Sanger sequencing of *SUOX*

(*continued on next page*)

Table 3 (*continued*)

Category of genetic conditions	Disease	Clinical features	Neuroimaging or EEG features	Genetic Investigations and Findings
	Molybdenum cofactor deficiency	Refractory neonatal seizures, feeding difficulties, rapidly progressive encephalopathy	Loss of gray-white matter differentiation, cerebral edema, extensive diffusion restriction on early MRI, progression to cystic encephalomalacia	Urine s-sulfocysteine (elevated) Sanger sequencing of *MOCS1* *MOCS2*
	Urea cycle disorders Carbamoylphosphate synthetase I, *N*-acetyl glutamate synthetase, Ornithine transcarbamylase, Argininosuccinate synthetase, Arginosuccinate lyase deficiencies	After being normal at birth, progressive lethargy, anorexia, hyper- or hypoventilation, hypothermia, seizures, neurologic posturing, coma (hyperammonemic encephalopathy due to brain edema)	Insular cortex, parietal, occipital, and frontal white matter diffusion restriction on MRI	Plasma amino acids, urine orotic acid. Based on biochemical profile, Sanger sequencing of *CPS1* *OTC* *ASS* *ASL*
	Maple syrup urine disease (MSUD)	Irritability, hypersomnolence, anorexia, progressive encephalopathy characterized with lethargy, apnea, opisthotonos, and reflexive "fencing" or "bicycling" movements, coma, central respiratory failure	Increased signal in cerebellar white matter, corticospinal tract, dorsal, brainstem, thalami on T2-weighted MRI images Extensive diffusion restriction involving white matter tracts	Plasma amino acids Sanger sequencing of *BCKDHA* *BCKDHB* *DBT*
	Organic acidurias Methylmalonic acidemia Propionic acidemia Isovaleric acidemia	After being normal at birth, progressive lethargy, poor feeding, vomiting, hypotonia, progress to encephalopathy and cardiorespiratory failure (hyperammonemic encephalopathy due to brain edema)	Increased signal in putamina and caudate, lobar infarcts, cerebellar bleed on T2-weighted MRI images	Acylcarnitine profile, urine organic acids Based on biochemical profile, Sanger sequencing of *PCCA, PCCB* *MMUT* *IVD*
	Pyridoxine-dependent epilepsy due to biallelic variants in *ALDH7A1*	NE, refractory seizures	Thin corpus callosum, mega cisterna magna	Urine AASA (elevated) Sanger sequencing of *ALDH7A1*
	Pyridoxamine 5′ oxidase (PNPO) deficiency	NE, refractory seizures	Normal	Sanger sequencing of *PNPO*
	Pyridoxal phosphate binding protein deficiency	NE, refractory seizures	Normal	Sanger sequencing of *PLPBP*
	Multiple carboxylase deficiency	NE, refractory seizures, hypotonia, vomiting	White matter abnormalities or cystic changes	Acylcarnitine profile, urine organic acids Based on biochemical profile, Sanger sequencing of *HLCS*
	Pyruvate dehydrogenase complex deficiency	NE, seizures, hypotonia, dysmorphic features (e.g. temporal narrowing, microcephaly, frontal bossing, wide nasal bridge, long philtrum)	Corpus callosum agenesis, ventriculomegaly, cerebral atrophy Subependymal pseudocysts	Lactic acidosis, normal lactate/pyruvate ratio Sanger sequencing of *PDHA1* *PDHX* *DLAT* *PDP1* or multigene panel or WES
	GABA transaminase deficiency	NE, seizures, hypotonia	Dysmyelination, cerebral atrophy on MRI Multifocal spikes, diffuse slowing, burst suppression in EEG	CSF free GABA (elevated) Sanger sequencing of *ABAT* or multigene panel or WES
	Zellweger spectrum disorder	NE, seizures, hypotonia, feeding difficulties, dysmorphic features (wide open anterior fontanelle, split sutures, hypertelorism, flat face, broad nasal bridge), hepatomegaly, liver and kidney cysts, jaundice	Cortical gyral abnormalities, germinolytic cysts Lipid peak on MRS in some cases	Plasma VLCFA (elevated), RBC plasmalogens Multigene panel for *PEX* genes or WES
	NDUFS4 disease *NDUFS6* disease *SUCLA2* disease *MTFMT* disease (Leigh syndrome)	NE, hypotonia, seizures	Bilateral symmetrical lesions within the brainstem and basal ganglia structures	Multigene panel or WES

AbbreviationsAASA = alpha-aminoadipic semialdehyde; CSF = cerebrospinal fluid; EEG = electroencephalogram; GABA = gamma aminobutyric acid; RBC = red blood cell; VLCFA = very long chain fatty acids; WES = whole exome sequencing.

several days. In half of affected infants, encephalopathy is present and neuroimaging reveals periventricular white matter involvement [88]. Diagnosis is made by PCR for viral RNA.

1.6. Metabolic derangements

Other factors which may affect the neurological status of a neonate are metabolic abnormalities related to electrolyte abnormalities. Many electrolyte imbalances are transient, and are related to the interplay of mother and fetus. Few are primarily due to intrinsic metabolite control in the neonate. All infants presenting with neonatal encephalopathy should have a glucose level and electrolytes checked at presentation. It is important to remember that electrolyte abnormalities frequently co-exist with HIE [89,90]. With the exception of profound hypoglycemia resulting in injury, if the level of encephalopathy is out of proportion to the electrolyte disturbance or persists following correction, alternative

Table 4
Clinical, imaging, and laboratory features of CNS Infectious causing neonatal encephalopathy.

Organism	Clinical features	Neuroimaging	Laboratory testing
E. coli	Chorioamnionitis Clinical sepsis	Hydrocephalus, cerebritis, infarction, brain abscess, subdural effusion or empyema, sinus thrombosis, ventriculitis	Blood and CSF culture PCR
GBS	Chorioamnionitis Clinical sepsis	Infarction, cerebritis, infarction, brain abscess, subdural effusion or empyema, sinus thrombosis, ventriculitis and hydrocephalus.	Blood and CSF culture PCR
Listeria	Lethargy, irritability, diarrhoea, poor feeding, vomiting, respiratory distress, characteristic skin rash (granulomatosis infantiseptica)	Hydrocephalus, abscesses, white matter injury	Blood and CSF culture
HSV	Seizures, skin-eye-mouth lesions, feeding difficulties, lethargy, irritability, tense fontanelle	Injury in watershed distribution, frontal & temporal lobe, corticospinal tracts involvement	CSF PCR HSV DNA Surface and lesion swabs
TORCHS	Seizures, microcephaly, fever, petechiae, deafness	Calcification, white matter injury	TORCH screen CMV PCR CSF VDRL
Parvovirus	Severe anemia, hydrops fetalis	Cortical dysplasia, heterotopia, hydrocephalus, calcifications, cerebellar hemorrhage	anti-NS1 antibodies, PCR
Parechovirus/ Enterovirus	Sepsis/shock Fever, irritability, diarrhoea, rash	Diffuse echogenicity periventricular and deep white matter, central gray nuclei and corticospinal tracts, cystic evolution	PCR EV and HPeV serum and CSF
Chikungunya virus	Poor feeding, rash, diarrhoea, brown skin discoloration	Periventricular leukomalacia, intraparenchymal haemorrhages	PCR viral RNA

Abbreviations: CSF = cerebrospinal fluid; *E.coli* = *Escherichia coli*; EV = enterovirus; *GBS* = group B *Streptococcus*; HPeV = human parechovirus; HSV = herpes simplex virus; NS1=Non-Structural Protein 1, the main non-structural protein in parvovirus B19; PCR = polymerase chain reaction; TORCHS = Toxoplasma gondii, rubella, cytomegalovirus (CMV), herpes simplex, syphilis, and others (human immunodeficiency virus, hepatitis B and C), VDRL=Venereal Disease Research Laboratory test.

causes must be considered.

Any infant with reduced alertness or oscillatory tremor of upper and lower limbs (jitteriness) should have a blood glucose check and measurement of electrolytes (including calcium, phosphate and magnesium). Transient hypotonia can be associated with reversible systemic conditions, such as electrolyte or endocrine abnormalities. One of the most common metabolic abnormalities seen in the neonatal period is hypoglycemia, due to the propensity of neonates to have a poor fasting tolerance, delay in initiation of feeding, or secondary to maternal diabetes.

Hypo- or hypercalcemia may also present in infants soon after birth with jitteriness, hyperreflexia, hypertonia and occasionally, seizures. In an infant with hypo- or hypercalcemia, measurement of serum calcium, parathyroid hormone, phosphorous, alkaline phosphatase, magnesium, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D levels, as well as urinary calcium excretion, can help to identify the underlying diagnosis. Common causes of hypercalcaemia include maternal vitamin D toxicity [91], subcutaneous fat necrosis [92], idiopathic infantile hypercalcemia [93], and Williams syndrome. In infants with hypocalcaemia, this may be secondary to transient hypoparathyroidism in growth-restricted infants or more persistent hypoparathyroidism (e.g. DiGeorge syndrome), infants of diabetic mothers, or maternal vitamin D deficiency. Inactivating and activating mutations of the calcium sensing receptor can present with neonatal hyper- or hypo-calcaemia, respectively [94].

Maternal administration of magnesium sulfate for pre-eclampsia may led to neonatal hypermagnesemia and hyporeactivity at birth; lower Apgar scores and hypotonia have been described [95]. The duration of symptoms of neonatal hypermagnesemia is dependent on the renal function of the neonate, as magnesium is primarily renally excreted.

1.7. Toxic exposures

Exposure to maternal drugs and toxins may also affect the neurological status of a neonate. A thorough history of maternal medications during pregnancy, or administered during labor or delivery should be sought in any infant with a reduced conscious level at birth. Both prescribed and illicit drugs can cause neurological symptoms in the infant. Any infant with hypertonia, hyperreflexia, or irritability not improving after 24–48 h of life should be screened for toxins and a further assessment of maternal recreational drug use should be performed. Recreational drugs inducing infant effects may include amphetamines, opiates, methadone, benzodiazepines, cannabinoids, cocaine metabolites and barbiturates. An infant with neonatal abstinence syndrome (NAS) may present with a continuous high-pitched cry, reduced sleep, poor feeding, overactive Moro reflex, tremors, and increased muscle tone. A thorough examination will differentiate from HIE, where tone is more typically reduced and Moro reflex is reduced or absent.

Obstetric administration of magnesium sulfate, opiates or general anesthesia may all suppress the infant's initial neurological status, leading to suppressed respiratory drive and need for resuscitation. However, this is usually short-lived and can be differentiated from HIE based on the history of administration and rapid recovery of the infant.

Neonatal effects have also been described with maternal use of antidepressants, including both tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRI) [96]. Maternal TCA use during pregnancy may result in an infant with irritability and abnormal tone. Serotonin toxicity may occur if a baby is breastfed by a mother on a high dose of an SSRI. Signs and symptoms may include tachypnea, jitteriness, irritability, hypertonia, fever, and compensated metabolic acidosis. However, for the majority of infants whose mothers are receiving SSRIs, neonatal abstinence does not occur [97]. Maternal use of anti-psychotic medication for schizophrenia may also cause neonatal effects, including low Apgar scores, hypotonia, or hypertonia, somnolence, and poor feeding [98]. However, many of these mothers have co-existing health morbidities and additional drug use, making it difficult to truly measure the direct effect of the anti-psychotic medications [99]. Maternal use of mood stabilizers such as lithium may also result in neonatal hypotonia and decreased deep tendon reflexes, in addition to more serious effects such as respiratory distress, apnea, cyanosis, cardiomegaly, cardiac arrhythmias [100].

2. Conclusions

Neonatal encephalopathy has a wide variety of etiologies. When taking care of a newborn with encephalopathy, it is important to consider conditions that may mimic HIE, including vascular conditions, neuromuscular disorders, brain malformations, genetic conditions, infections, metabolic and toxic disturbances. It is also important to consider that HIE can co-exist with other causes of NE, including electrolyte derangements and vascular injury. While there are distinguishing

features of the clinical history and physical examination, there can often be considerable similarities in the presentation of various causes of NE. Targeted investigations guided by clinical suspicion can help to differentiate these causes, and tailor the treatment to the specific diagnosis. Therapeutic hypothermia should not be withheld in cases where the cause of NE is unknown and HIE is suspected, as the substantial benefits of cooling for HIE outweigh the risks of this therapy in cases where a different cause for NE is ultimately found.

3. Practice points

- Neonatal encephalopathy (NE) is a clinical diagnosis which may arise from numerous etiologies
- HIE may be distinguished from NE due to other causes using the history, physical and neurological exam, and investigations

4. Research directions

- Evaluate the yield of broad genetic testing, such as WES or WGS, in all neonates with NE
- Develop and validate bedside tools for rapid, accurate diagnosis of various causes of NE

References

[1] Volpe JJ. Neonatal encephalopathy: an inadequate term for hypoxic-ischemic encephalopathy. Ann Neurol 2012;72(2):156–66. https://doi.org/10.1002/ana.23647.
[2] Chalak L, Ferriero DM, Gressens P, Molloy E, Bearer C. A 20 years conundrum of neonatal encephalopathy and hypoxic ischemic encephalopathy: are we closer to a consensus guideline? Pediatr Res 2019;86(5):548–9. https://doi.org/10.1038/s41390-019-0547-9.
[3] Executive summary: neonatal encephalopathy and neurologic outcome, second edition. Report of the American College of Obstetricians and Gynecologists' task force on neonatal encephalopathy. Obstet Gynecol 2014;123(4):896–901. https://doi.org/10.1097/01.AOG.0000445580.65983.d2.
[4] Hankins GDV, Speer M. Defining the pathogenesis and pathophysiology of neonatal encephalopathy and cerebral palsy. Obstet Gynecol 2003;102(3):628–36. https://doi.org/10.1016/s0029-7844(03)00574-x.
[5] Douglas-Escobar M, Weiss MD. Hypoxic-ischemic encephalopathy: a review for the clinician. JAMA Pediatr 2015;169(4):397–403. https://doi.org/10.1001/jamapediatrics.2014.3269.
[6] Martinello K, Hart AR, Yap S, Mitra S, Robertson NJ. Management and investigation of neonatal encephalopathy: 2017 update. Arch Dis Child Fetal Neonatal Ed 2017;102(4):F346–58. https://doi.org/10.1136/archdischild-2015-309639.
[7] Mercuri E, Ricci D, Pane M, Baranello G. The neurological examination of the newborn baby Early Hum Dev 2005;81(12):947–56. https://doi.org/10.1016/j.earlhumdev.2005.10.007.
[8] Chau V, Poskitt KJ, Dunham CP, Hendson G, Miller SP. Magnetic resonance imaging in the encephalopathic term newborn. Curr Pediatr Rev 2014;10(1):28–36. https://doi.org/10.2174/1573396310011404081203336.
[9] Ferriero DM. The vulnerable newborn brain: imaging patterns of acquired perinatal injury. Neonatology 2016;109(4):345–51. https://doi.org/10.1159/000444896.
[10] Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev 2013;1:CD003311. https://doi.org/10.1002/14651858.CD003311.pub3.
[11] Rossor T, Arichi T, Bhate S, Hart AR, Raman Singh R. Anticoagulation in the management of neonatal cerebral sinovenous thrombosis: a systematic review and meta-analysis. Dev Med Child Neurol 2018;60(9):884–91. https://doi.org/10.1111/dmcn.13760.
[12] Colditz MJ, Lai MM, Cartwright DW, Colditz PB. Subgaleal haemorrhage in the newborn: a call for early diagnosis and aggressive management. J Paediatr Child Health 2015;51(2):140–6. https://doi.org/10.1111/jpc.12698.
[13] Luo L, Chen D, Qu Y, Wu J, Li X, Mu D. Association between hypoxia and perinatal arterial ischemic stroke: a meta-analysis. PloS One 2014;9(2):e90106. https://doi.org/10.1371/journal.pone.0090106.
[14] Martinez-Biarge M, Cheong JLY, Diez-Sebastian J, Mercuri E, Dubowitz LMS, Cowan FM. Risk factors for neonatal arterial ischemic stroke: the importance of the intrapartum period. J Pediatr 2016;173:62–8. https://doi.org/10.1016/j.jpeds.2016.02.064. e1.
[15] Adami RR, Grundy ME, Poretti A, Felling RJ, Lemmon M, Graham EM. Distinguishing arterial ischemic stroke from hypoxic-ischemic encephalopathy in the neonate at birth. Obstet Gynecol 2016;128(4):704–12. https://doi.org/10.1097/AOG.0000000000001631.
[16] Cowan F, Rutherford M, Groenendaal F, et al. Origin and timing of brain lesions in term infants with neonatal encephalopathy. Lancet (London, England) 2003;361(9359):736–42. https://doi.org/10.1016/S0140-6736(03)12658-X.
[17] Low E, Mathieson SR, Stevenson NJ, et al. Early postnatal EEG features of perinatal arterial ischaemic stroke with seizures. PloS One 2014;9(7):e100973. https://doi.org/10.1371/journal.pone.0100973.
[18] Rafay MF, Cortez MA, de Veber GA, et al. Predictive value of clinical and EEG features in the diagnosis of stroke and hypoxic ischemic encephalopathy in neonates with seizures. Stroke 2009;40(7):2402–7. https://doi.org/10.1161/STROKEAHA.109.547281.
[19] Radicioni M, Bini V, Chiarini P, et al. Cerebral sinovenous thrombosis in the asphyxiated cooled infants: a prospective observational study. Pediatr Neurol 2017;66:63–8. https://doi.org/10.1016/j.pediatrneurol.2016.09.006.
[20] Al Yazidi G, Boudes E, Tan X, Saint-Martin C, Shevell M, Wintermark P. Intraventricular hemorrhage in asphyxiated newborns treated with hypothermia: a look into incidence, timing and risk factors. BMC Pediatr 2015;15:106. https://doi.org/10.1186/s12887-015-0415-7.
[21] Zhu X, Liu M, Gong X, et al. Transcranial color-coded sonography for the detection of cerebral veins and sinuses and diagnosis of cerebral venous sinus thrombosis. Ultrasound Med Biol 2019;45(10):2649–57. https://doi.org/10.1016/j.ultrasmedbio.2019.06.419.
[22] Grunt S, Wingeier K, Wehrli E, et al. Cerebral sinus venous thrombosis in Swiss children. Dev Med Child Neurol 2010;52(12):1145–50. https://doi.org/10.1111/j.1469-8749.2010.03722.x.
[23] Lebas A, Chabrier S, Fluss J, et al. EPNS/SFNP guideline on the anticoagulant treatment of cerebral sinovenous thrombosis in children and neonates. Eur J Paediatr Neurol 2012;16(3):219–28. https://doi.org/10.1016/j.ejpn.2012.02.005.
[24] Morton SU, Prabhu SP, Lidov HGW, et al. AIFM1 mutation presenting with fatal encephalomyopathy and mitochondrial disease in an infant. Cold Spring Harbor Molecular Case Studies 2017;3(2):a001560. https://doi.org/10.1101/mcs.a001560.
[25] Zagaglia S, Selch C, Nisevic JR, et al. Neurologic phenotypes associated with COL4A1/2 mutations: expanding the spectrum of disease. Neurology 2018;91(22). https://doi.org/10.1212/WNL.0000000000006567. e2078-e2088.
[26] Vermeulen RJ, Peeters-Scholte C, Van Vugt JJM, et al. Fetal origin of brain damage in 2 infants with a COL4A1 mutation: fetal and neonatal MRI. Neuropediatrics 2011;42(1):1–3. https://doi.org/10.1055/s-0031-1275343.
[27] Malarbi S, Gunn-Charlton JK, Burnett AC, et al. Outcome of vein of Galen malformation presenting in the neonatal period. Arch Dis Child 2019;104(11):1064–9. https://doi.org/10.1136/archdischild-2018-316495.
[28] Delaney HM, Rooks VJ, Wolfe SQ, Sawyer TL. Term neonate with intracranial hemorrhage and hereditary hemorrhagic telangiectasia: a case report and review of the literature. J Perinatol 2012;32(8):642–4. https://doi.org/10.1038/jp.2011.146.
[29] Giorgi L, Durand P, Morin L, et al. Management and outcomes of neonatal arteriovenous brain malformations with cardiac failure: a 17 Years' experience in a tertiary referral center. J Pediatr 2020;218:85–91. https://doi.org/10.1016/j.jpeds.2019.10.090. e2.
[30] Ejike O, Odume C, Ekwochi U, Ndu I, Imanyikwa U. A rare type of congenital Sturge-Weber Syndrome: presenting with history of perinatal asphyxia. Clin Case Rep 2016;4(8):725–7. https://doi.org/10.1002/ccr3.561.
[31] El-Dib M, Parziale MP, Johnson L, et al. Encephalopathy in neonates with subgaleal hemorrhage is a key predictor of outcome. Pediatr Res 2019;86(2):234–41. https://doi.org/10.1038/s41390-019-0400-1.
[32] Glass HC. Hypoxic-ischemic encephalopathy and other neonatal encephalopathies. Continuum 2018;24:57–71. https://doi.org/10.1212/CON.0000000000000557 (1, Child Neurology).
[33] Fay AJ. Neuromuscular diseases of the newborn. Semin Pediatr Neurol 2019;32:100771. https://doi.org/10.1016/j.spen.2019.08.007.
[34] Echenne B, Bassez G. Congenital and infantile myotonic dystrophy. Handb Clin Neurol 2013;113:1387–93. https://doi.org/10.1016/B978-0-444-59565-2.00009-5.
[35] Yum K, Wang ET, Kalsotra A. Myotonic dystrophy: disease repeat range, penetrance, age of onset, and relationship between repeat size and phenotypes. Curr Opin Genet Dev 2017;44:30–7. https://doi.org/10.1016/j.gde.2017.01.007.
[36] Durbeej M. Laminin-α2 chain-deficient congenital muscular dystrophy: pathophysiology and development of treatment. Curr Top Membr 2015;76:31–60. https://doi.org/10.1016/bs.ctm.2015.05.002.
[37] Dowling JJ, D Gonorazky H, Cohn RD, Campbell C. Treating pediatric neuromuscular disorders: the future is now. Am J Med Genet 2018;176(4):804–41. https://doi.org/10.1002/ajmg.a.38418.
[38] Gonçalves FG, Freddi T de AL, Taranath A, et al. Tubulinopathies. *Top Magn Reson Imaging* 2018;27(6):395–408. https://doi.org/10.1097/RMR.0000000000000188.
[39] Bahi-Buisson N, Poirier K, Fourniol F, et al. The wide spectrum of tubulinopathies: what are the key features for the diagnosis? Brain 2014;137(Pt 6):1676–700. https://doi.org/10.1093/brain/awu082.
[40] Bahi-Buisson N, Guerrini R. Diffuse malformations of cortical development. Handb Clin Neurol 2013;111:653–65. https://doi.org/10.1016/B978-0-444-52891-9.00068-3.
[41] Dobyns WB, Curry CJ, Hoyme HE, Turlington L, Ledbetter DH. Clinical and molecular diagnosis of Miller-Dieker syndrome. Am J Hum Genet 1991;48(3):584–94.

[42] Hahn JS, Barnes PD. Neuroimaging advances in holoprosencephaly: refining the spectrum of the midline malformation. Am J Med Genet C Semin Med Genet 2010;154C(1):120–32. https://doi.org/10.1002/ajmg.c.30238.
[43] Dubourg C, Bendavid C, Pasquier L, Henry C, Odent S, David V. Holoprosencephaly. *Orphanet J Rare Dis*. 2007;2:8. https://doi.org/10.1186/1750-1172-2-8.
[44] Brancati F, Dallapiccola B, Valente EM. Joubert Syndrome and related disorders. Orphanet J Rare Dis 2010;5:20. https://doi.org/10.1186/1750-1172-5-20.
[45] Gleeson JG, Keeler LC, Parisi MA, et al. Molar tooth sign of the midbrain-hindbrain junction: occurrence in multiple distinct syndromes. Am J Med Genet 2004;125A(2):125–34. https://doi.org/10.1002/ajmg.a.20437. discussion 117.
[46] Maria BL, Boltshauser E, Palmer SC, Tran TX. Clinical features and revised diagnostic criteria in Joubert syndrome. J Child Neurol 1999;14(9):583–90. https://doi.org/10.1177/088307389901400906. discussion 590-591.
[47] Cormand B, Pihko H, Bayés M, et al. Clinical and genetic distinction between Walker-Warburg syndrome and muscle-eye-brain disease. Neurology 2001;56(8):1059–69. https://doi.org/10.1212/wnl.56.8.1059.
[48] Fukuyama Y. Congenital muscular dystrophies: an update. J Child Neurol 1999;14(1):28–30.
[49] Toda T, Kobayashi K, Kondo-Iida E, Sasaki J, Nakamura Y. The Fukuyama congenital muscular dystrophy story. Neuromuscul Disord 2000;10(3):153–9. https://doi.org/10.1016/s0960-8966(99)00109-1.
[50] Hirsch JF, Pierre-Kahn A, Renier D, Sainte-Rose C, Hoppe-Hirsch E. The Dandy-Walker malformation. A review of 40 cases. J Neurosurg 1984;61(3):515–22. https://doi.org/10.3171/jns.1984.61.3.0515.
[51] Pascual-Castroviejo I, Velez A, Pascual-Pascual SI, Roche MC, Villarejo F. Dandy-Walker malformation: analysis of 38 cases. Childs Nerv Syst 1991;7(2):88–97. https://doi.org/10.1007/BF00247863.
[52] Enns GM. Inborn errors of metabolism masquerading as hypoxic-ischemic encephalopathy. NeoReviews 2005;6(12):e549–58. https://doi.org/10.1542/neo.6-12-e549.
[53] Bruun TUJ, DesRoches C-L, Wilson D, et al. Prospective cohort study for identification of underlying genetic causes in neonatal encephalopathy using whole-exome sequencing. Genet Med 2018;20(5):486–94. https://doi.org/10.1038/gim.2017.129.
[54] Daoud H, Luco SM, Li R, et al. Next-generation sequencing for diagnosis of rare diseases in the neonatal intensive care unit. CMAJ (Can Med Assoc J) 2016;188(11):E254–60. https://doi.org/10.1503/cmaj.150823.
[55] Soden SE, Saunders CJ, Willig LK, et al. Effectiveness of exome and genome sequencing guided by acuity of illness for diagnosis of neurodevelopmental disorders. Sci Transl Med 2014;6(265). https://doi.org/10.1126/scitranslmed.3010076. 265ra168.
[56] Yang L, Chen X, Liu X, et al. Clinical features and underlying genetic causes in neonatal encephalopathy: a large cohort study. *Clin Genet*. Published online July 2020;26. https://doi.org/10.1111/cge.13818.
[57] Willis TA, Davidson J, Gray RG, Poulton K, Ramani P, Whitehouse W. Cytochrome oxidase deficiency presenting as birth asphyxia. Dev Med Child Neurol 2000;42(6):414–7. https://doi.org/10.1017/s0012162200000761.
[58] Mercimek-Mahmutoglu S, Horvath GA, Coulter-Mackie M, et al. Profound neonatal hypoglycemia and lactic acidosis caused by pyridoxine-dependent epilepsy. Pediatrics 2012;129(5):e1368–1372. https://doi.org/10.1542/peds.2011-0123.
[59] Topcu M, Coskun T, Haliloglu G, Saatci I. Molybdenum cofactor deficiency: report of three cases presenting as hypoxic-ischemic encephalopathy. J Child Neurol 2001;16(4):264–70. https://doi.org/10.1177/088307380101600406.
[60] Escobar LF, Wagner S, Tucker M, Wareham J. Neonatal presentation of lethal neuromuscular glycogen storage disease type IV. J Perinatol 2012;32(10):810–3. https://doi.org/10.1038/jp.2011.178.
[61] Braga SE, Gerber A, Meier C, et al. Severe neonatal asphyxia due to X-linked centronuclear myopathy. Eur J Pediatr 1990;150(2):132–5. https://doi.org/10.1007/BF02072056.
[62] Weeke LC, Brilstra E, Braun KP, et al. Punctate white matter lesions in full-term infants with neonatal seizures associated with SLC13A5 mutations. Eur J Paediatr Neurol 2017;21(2):396–403. https://doi.org/10.1016/j.ejpn.2016.11.002.
[63] Chakkarapani E, Davis J, Thoresen M. Therapeutic hypothermia delays the C-reactive protein response and suppresses white blood cell and platelet count in infants with neonatal encephalopathy. Arch Dis Child Fetal Neonatal Ed 2014;99(6):F458–63. https://doi.org/10.1136/archdischild-2013-305763.
[64] Tann CJ, Nkurunziza P, Nakakeeto M, et al. Prevalence of bloodstream pathogens is higher in neonatal encephalopathy cases vs. Controls using a novel panel of real-time PCR assays. PloS One 2014;9(5). https://doi.org/10.1371/journal.pone.0097259.
[65] Mallard C, Wang X. Infection-induced vulnerability of perinatal brain injury. Neurol Res Int 2012;2012:102153. https://doi.org/10.1155/2012/102153.
[66] Nelson KB, Leviton A. How much of neonatal encephalopathy is due to birth asphyxia? Am J Dis Child 1991;145(11):1325–31. https://doi.org/10.1001/archpedi.1991.02160110117034.
[67] Aslam S, Strickland T, Molloy EJ. Neonatal encephalopathy: need for recognition of multiple etiologies for optimal management. Front Pediatr 2019;7:142. https://doi.org/10.3389/fped.2019.00142.
[68] Martinello KA, Meehan C, Avdic-Belltheus A, et al. Acute LPS sensitization and continuous infusion exacerbates hypoxic brain injury in a piglet model of neonatal encephalopathy. Sci Rep 2019;9(1):10184. https://doi.org/10.1038/s41598-019-46488-y.
[69] Nelson KB, Grether JK. Potentially asphyxiating conditions and spastic cerebral palsy in infants of normal birth weight. Am J Obstet Gynecol 1998;179(2):507–13. https://doi.org/10.1016/s0002-9378(98)70387-4.
[70] O'Hare FM, Watson RWG, O'Neill A, et al. Serial cytokine alterations and abnormal neuroimaging in newborn infants with encephalopathy. Acta Paediatr 2017;106(4):561–7. https://doi.org/10.1111/apa.13745.
[71] Nelson KB, Willoughby RE. Infection, inflammation and the risk of cerebral palsy. Curr Opin Neurol 2000;13(2):133–9. https://doi.org/10.1097/00019052-200004000-00004.
[72] Willoughby RE, Nelson KB. Chorioamnionitis and brain injury. Clin Perinatol 2002;29(4):603–21. https://doi.org/10.1016/s0095-5108(02)00058-1.
[73] Tann CJ, Martinello KA, Sadoo S, et al. Neonatal encephalopathy with group B streptococcal disease worldwide: systematic review, investigator group datasets, and meta-analysis. Clin Infect Dis 2017;65(suppl_2):S173–89. https://doi.org/10.1093/cid/cix662.
[74] Parker S-J, Kuzniewicz M, Niki H, Wu YW. Antenatal and intrapartum risk factors for hypoxic-ischemic encephalopathy in a US birth cohort. J Pediatr 2018;203:163–9. https://doi.org/10.1016/j.jpeds.2018.08.028.
[75] Nelson KB, Bingham P, Edwards EM, et al. Antecedents of neonatal encephalopathy in the Vermont Oxford network encephalopathy registry. Pediatrics 2012;130(5):878–86. https://doi.org/10.1542/peds.2012-0714.
[76] Kralik SF, Kukreja MK, Paldino MJ, Desai NK, Vallejo JG. Comparison of CSF and MRI findings among neonates and infants with E coli or group B streptococcal meningitis. AJNR Am J Neuroradiol 2019;40(8):1413–7. https://doi.org/10.3174/ajnr.A6134.
[77] Falck M, Osredkar D, Maes E, et al. Hypothermic neuronal rescue from infection-sensitised hypoxic-ischaemic brain injury is pathogen dependent. Dev Neurosci 2017;39(1–4):238–47. https://doi.org/10.1159/000455838.
[78] Wintermark P, Boyd T, Gregas MC, Labrecque M, Hansen A. Placental pathology in asphyxiated newborns meeting the criteria for therapeutic hypothermia. Am J Obstet Gynecol 2010;203(6). https://doi.org/10.1016/j.ajog.2010.08.024. 579. e1-9.
[79] Grover SB, Mahato S, Chellani H, Saluja S, Rajalakshmi GP. Disseminated intravascular coagulation with intracranial haematoma in neonatal congenital syphilis. J Trop Pediatr 2011;57(4):315–8. https://doi.org/10.1093/tropej/fmq088.
[80] Charlier C, Disson O, Lecuit M. Maternal-neonatal listeriosis. Virulence 2020;11(1):391–7. https://doi.org/10.1080/21505594.2020.1759287.
[81] Sapuan S, Kortsalioudaki C, Anthony M, et al. Neonatal listeriosis in the UK 2004-2014. J Infect 2017;74(3):236–42. https://doi.org/10.1016/j.jinf.2016.11.007.
[82] Lee DT, Park CJ, Peterec S, Morotti R, Cowles RA. Outcomes of neonates with listeriosis supported with extracorporeal membrane oxygenation from 1991 to 2017. J Perinatol 2020;40(1):105–11. https://doi.org/10.1038/s41372-019-0534-3.
[83] de Vries LS. Viral infections and the neonatal brain. Semin Pediatr Neurol 2019;32:100769. https://doi.org/10.1016/j.spen.2019.08.005.
[84] Kidokoro H, de Vries LS, Ogawa C, et al. Predominant area of brain lesions in neonates with herpes simplex encephalitis. J Perinatol 2017;37(11):1210–4. https://doi.org/10.1038/jp.2017.114.
[85] Allen UD, Robinson JL. Canadian Paediatric Society, Infectious Diseases and Immunization Committee. Prevention and management of neonatal herpes simplex virus infections. Paediatr Child Health 2014;19(4):201–12. https://doi.org/10.1093/pch/19.4.201.
[86] Schreiber R, Wolpin J, Koren G. Determinants of aciclovir-induced nephrotoxicity in children. Paediatr Drugs 2008;10(2):135–9. https://doi.org/10.2165/00148581-200810020-00008.
[87] Pistorius LR, Smal J, de Haan TR, et al. Disturbance of cerebral neuronal migration following congenital parvovirus B19 infection. Fetal Diagn Ther 2008;24(4):491–4. https://doi.org/10.1159/000180119.
[88] Maria A, Vallamkonda N, Shukla A, Bhatt A, Sachdev N. Encephalitic presentation of neonatal Chikungunya: a case series. Indian Pediatr 2018;55(8):671–4.
[89] Ilves P, Kiisk M, Soopõld T, Talvik T. Serum total magnesium and ionized calcium concentrations in asphyxiated term newborn infants with hypoxic-ischaemic encephalopathy. Acta Paediatr 2000;89(6):680–5. https://doi.org/10.1080/080352500750043990.
[90] Vayalthrikkovil S, Bashir R, Espinoza M, Irvine L, Scott JN, Mohammad K. Serum calcium derangements in neonates with moderate to severe hypoxic ischemic encephalopathy and the impact of therapeutic hypothermia: a cohort study. J Matern Fetal Neonatal Med 2020;33(6):935–40. https://doi.org/10.1080/14767058.2018.1510911.
[91] Reynolds A, O'Connell SM, Kenny LC, Dempsey E. Transient neonatal hypercalcaemia secondary to excess maternal vitamin D intake: too much of a good thing. BMJ Case Rep 2017;2017. https://doi.org/10.1136/bcr-2016-219043.
[92] Farooque A, Moss C, Zehnder D, Hewison M, Shaw NJ. Expression of 25-hydroxyvitamin D3-1alpha-hydroxylase in subcutaneous fat necrosis. Br J Dermatol 2009;160(2):423–5. https://doi.org/10.1111/j.1365-2133.2008.08844.x.
[93] Schlingmann KP, Kaufmann M, Weber S, et al. Mutations in CYP24A1 and idiopathic infantile hypercalcemia. N Engl J Med 2011;365(5):410–21. https://doi.org/10.1056/NEJMoa1103864.
[94] Hendy GN, Li L D'Souza, Yang B, Canaff L, Cole DE. Mutations of the calcium-sensing receptor (CASR) in familial hypocalciuric hypercalcemia, neonatal severe hyperparathyroidism, and autosomal dominant hypocalcemia. Hum Mutat 2000;16(4):281–96. 10.1002/1098-1004(200010)16:4<281::AID-HUMU1>3.0.CO;2-A.

[95] Abbassi-Ghanavati M, Alexander JM, McIntire DD, Savani RC, Leveno KJ. Neonatal effects of magnesium sulfate given to the mother. Am J Perinatol 2012; 29(10):795–9. https://doi.org/10.1055/s-0032-1316440.

[96] Gentile S. On categorizing gestational, birth, and neonatal complications following late pregnancy exposure to antidepressants: the prenatal antidepressant exposure syndrome. CNS Spectr 2010;15(3):167–85. https://doi.org/10.1017/s1092852900027449.

[97] McLean K, Murphy KE, Dalfen A, Shea AK. The effect of maternal antidepressants on third trimester uteroplacental hemodynamics and the neonatal abstinence syndrome: a retrospective cohort study. Arch Womens Ment Health 2019;22(6): 791–7. https://doi.org/10.1007/s00737-019-00954-8.

[98] Gentile S. Antipsychotic therapy during early and late pregnancy. A systematic review. Schizophr Bull 2010;36(3):518–44. https://doi.org/10.1093/schbul/sbn107.

[99] Ornoy A, Weinstein-Fudim L, Ergaz Z. Antidepressants, antipsychotics, and mood stabilizers in pregnancy: what do we know and how should we treat pregnant women with depression. Birth Defects Res 2017;109(12):933–56. https://doi.org/10.1002/bdr2.1079.

[100] Pinelli JM, Symington AJ, Cunningham KA, Paes BA. Case report and review of the perinatal implications of maternal lithium use. Am J Obstet Gynecol 2002;187 (1):245–9. https://doi.org/10.1067/mob.2002.123610.