Unexpected neurologic events in the maternity ward

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Abstract

Unexpected neurologic events in the maternity ward are highly suggestive of seizure activity in the newborn infant. Acute provoked symptomatic seizures associated with an early ischaemic or haemorrhagic brain insult account for more than 70% of neonatal seizures. Neonatal onset of infantile epilepsy occurs much less often. These two pathologic entities represent different types of seizures, different semiology, and different response to anti-epileptic drugs. Recognising clinical seizures in a newborn infant can be challenging and must be confirmed with video EEG monitoring. Seizures in a healthy term neonate necessitate admission to a neonatal intensive care unit. Investigating the aetiology and providing a prognosis to the parents require special expertise, including specific laboratory testing, magnetic resonance imaging of the brain and neurophysiological analysis. The purpose of this review is to highlight the aetiology and the clinical presentation of seizures in the apparently healthy term neonate and to propose a network management algorithm between paediatricians, neonatologists, and neuro-paediatricians.

Introduction

Neonatal seizures are not uncommon; the overall incidence is reported as 1-3.5/1000 of all live births (1,2). More than 70% of neonatal seizures consist of acute provoked seizures and are symptomatic of an acute brain insult such as perinatal asphyxia, stroke, or intra-cranial haemorrhage (2). In contrast, only 10% of neonatal seizures consist of early onset infantile epilepsy due to a genetic, metabolic or malformative origin (2,3).

Acute provoked symptomatic seizures and neonatal onset infantile epilepsy are two different pathologic entities. They represent different types of crises, different EEG traces, respond to different anti-epileptic drugs and need different explorations. Therefore, they must be differentiated early during the neonatal course (4).

Upon a severe perinatal asphyxiating insult, neurological depression is mostly obvious, and neonates must be admitted to a neonatal intensive care unit (NICU) to facilitate close monitoring. In contrast, arterial ischaemic stroke, cerebral sinovenous thrombosis (CSVT) and intra-cranial haemorrhage typically occur during the first hours or days of life in initially healthy term neonates at the maternity ward (5). Moreover, acute provoked symptomatic seizures in the context of these pathologies may be less obvious, as the seizures are numerous but short lasting, subtle, and even sometimes electrographic-only. Such subtle seizures can thus be missed or misinterpreted (6,7). Missing the occurrence of neonatal seizures can result in a lack of diagnosis, delayed treatment, remote neurologic sequelae, and remote epilepsy (8). This is more important as the length of stay in our Belgian maternity hospitals has recently been reduced to 48 hours.

On the other hand, rapidly controlling an epileptic crisis with an unspecific drug and without any EEG documentation or trained observation compromises a correct diagnosis and treatment (4). Seizures in a well-doing term neonate are thus a neurologic emergency and need an admission to a NICU.

In this review, we emphasize the importance of an early recognition of the seizures, the importance of an appropriate treatment, and we highlight the mandatory diagnostic pathways. We propose a care algorithm involving paediatricians, neonatologists, and neuro-paediatricians.

Clinical manifestations of neonatal seizures

Neonatal seizures (NS) are defined as a paroxysmal electro-clinical phenomenon characterized by the transient occurrence of signs and symptoms that are caused by an excessive or synchronous neuronal activity within the brain (9).

The clinical diagnosis of NS may be very challenging. Indeed, non-epileptic paroxysmal manifestations such as tremor, jitteriness, clonus, non-seizure sucking and repetitive movements during sleep are frequent in the neonatal period and can be misdiagnosed as seizure-related manifestations (6,10,11). Benign neonatal sleep myoclonus is another frequent condition characterized by myoclonus during sleep in a healthy newborn, resolving while awake and disappearing within the first months of life (3).

In 2017, the International League Against Epilepsy introduced a revised classification of seizure types including specific guidelines for NS (12). This new classification is based on clinical symptoms as well as EEG, depending on the predominant seizure type: electrographic-only seizures (i.e., clinically silent seizures) and electro-clinical seizures (including motor, non-motor, or sequential presentation) (9). Clinical events without an EEG correlate are not included in this new neonatal classification.

Clinically silent seizures represent most of the neonatal seizures: they are subclinical or electrographic only. Unless the seizure originates in or migrates to the motor cortex, the newborn will not present abnormal movements. As the newborn cannot express sensory phenomena, a seizure that is limited in a non-motor area will resume in subtle clinical manifestations, for instance recurrent apnoea (3,6,13).

Electro-clinical motor seizures include focal clonic seizures, focal tonic seizures, epileptic spasms, myoclonic seizures, and automatisms. Electro-clinical non-motor seizures include autonomic and behavioural arrest seizures. (Table 1).

Clonic seizures are the most frequent motor seizures and consist of rhythmic and repeated contractions of limbs, face, or trunk muscles. They can be focal, migrant, or multifocal. Tonic seizures are characterized by a progressive and asymmetrical stiffening of the trunk or limb. Epileptic spasms manifest as

a flexion or extension of the muscles of the trunk or extremities, they are usually associated with neonatal-onset epilepsy. Myoclonic seizures are brief contractions of muscles groups in the limb, trunk, or face. A differential diagnosis with benign sleep myoclonus is required. Apart from these typical seizure manifestations, more subtle and non-specific clinical signs should also lead to consider the possibility of an underlying seizure activity. Oro-lingual and orbito-ocular movements are suggestive of subtle seizures and unusual repetitive movements such as cycling, and boxing are suggestive of automatisms. Clinical signs of autonomic seizures include changes in heart rate or breathing pattern (e.g., apnoea), pupillary dilatation, or cutaneous flushing. Behavioural arrest seizures manifest as a sudden decrease or interruption of ongoing motor activity. Although frequent in neonates, subtle, autonomic, and behavioural arrest seizures usually present with other accompanying seizure symptoms (3).

Table 1 : 2017 ILAE classification of neonatal seizures (based on Shellhaas 2019 and Pressler 2021)

Type	Features	Aetiology	Comments
Clonic	*Repetitive, rhythmic contraction, involving the same muscle group, either* symmetric or asymmetric. Unifocal, multifocal or migratory presentations are described.	*Typical seizure type in* neonatal stroke or cerebral haemorrhage; may also be seen in HIE and in neonatal onset epilepsies.	*Most reliably recognized* clinical seizure type.
Tonic	Sustained increase in muscle contraction, lasting a few seconds to minutes, with asymmetric limb posture.	Often seen in genetic neonatal onset epilepsies.	
Epileptic spasms	Sudden flexion, extension, or mixed extension-flexion of predominantly proximal and truncal muscles.	May be seen in inborn errors of metabolism or neonatal onset epilepsies.	Rare and brief in neonates. Limited forms may occur: Grimacing, head nodding, or subtle eye movements.
Myoclonic	Sudden and brief involuntary single or multiple contraction(s) of muscles(s) or muscle groups of variable topography (axial, proximal limb, distal).	Typical seizure type in errors of metabolism and preterm infant; may also be seen in neonatal onset epilepsies such early myoclonic epilepsy of infancy.	Benign sleep myoclonus is a non-seizure condition that needs to be differentiated from myoclonic seizures.
Automatisms	More or less coordinated motor activity with impaired cognition: eye deviation, sucking, chewing, boxing/cycling movements or purposeless complex movements.	Seen in HIE and preterm infant; often part of sequential seizures.	Very common but rarely isolated without other associated motor manifestation; typically oral in neonates.
Sequential	Sequence of signs, symptoms, and EEG changes at different times. No predominant feature determined.	Often seen in genetic neonatal onset epilepsies.	Often with changing lateralization
Autonomic	Distinct alteration of autonomic nervous system function involving cardiovascular, pupillary, gastrointestinal, sudomotor, vasomotor, or thermoregulatory functions.	Seen in intraventricular haemorrhage as well as with temporal or occipital lobe lesions.	Rarely truly isolated but typically concomitant motor manifestations.
Behavioural arrest	Arrest of activities, freezing, immobilization, as in behaviour arrest seizure		Rarely isolated.
Electrographic only	Subclinical, without clinical manifestation. Electro-clinical dissociation is frequent in neonates.	Seen in HIE and preterm infant.	Facilitated by AEDs and in case of severe encephalopathy.
Unclassified	Due to inadequate information or unusual clinical features		

Aetiology of neonatal seizures

It is important to identify as soon as possible the origin of the seizures in a newborn infant. Indeed, the investigations, the molecule chosen for the treatment and the duration of the treatment will essentially depend on the aetiology of the seizures.

A. *Acute provoked symptomatic seizures*

Acute provoked symptomatic seizures are clinical seizures occurring at the time of, or in close temporal relationship with a documented central nervous system (CNS) or systemic insult, which may be metabolic, toxic, structural, infectious, or inflammatory in origin.

1. *Perinatal asphyxia* is the most common cause of neonatal symptomatic seizures (2). This paper focusses on the pathologies affecting the apparently healthy newborn in the maternity ward; asphyxiated newborns suffering from hypoxic-ischaemic encephalopathy should be referred to a NICU. Whilst some newborns with signs of mild to moderate asphyxia are admitted to the maternity ward, they may exceptionally present with seizures.

2. *Perinatal arterial ischaemic stroke (PAIS)* is the second most common cause of symptomatic seizures (2,14). PAIS occurs in about 1 in 2,300-5,000 live births. There is no specific pathology related to PAIS, and as such, PAIS is more likely to result from multifactorial conditions. In most cases, there is no particular maternal history, and the pregnancy was normal. Nevertheless, certain circumstances surrounding the birth of newborns with PAIS are found: a history of infertility, primiparity, pre-eclampsia, gestational diabetes, chorioamnionitis, signs of foetal distress, emergency caesarean section, male sex, neonatal polycythaemia, neonatal hypoglycaemia, and neonatal infection. Its pathophysiology is currently better understood, and it incriminates in most cases the occlusion of a cerebral arterial blood vessel by a clot originating from the placenta. The transitional circulation during the early hours of life with high pressures in the right chambers of the heart favours the opening of the foramen oval. This situation allows the formation of clots that can migrate directly from the placental interface into the arterial circulation. The blood flow dynamics preferentially direct the clots to the left middle cerebral artery. The other hypothesis is traumatic, i.e., an arterial lesion can occur within the context of extraction forces onto the head during the birth process (5).

The initial clinical manifestations of PAIS are most frequently motor (90%): lateralized focal or hemi-corporeal clonic seizures can occur during the second and/or third day of life. In addition, many newborns with PAIS present with apnoeic spells or cyanotic attacks. Less frequently, seizures are vegetative in nature, such as bradycardia, skin flush, hiccup or dysregulation of blood pressure or temperature. For instance, an alarming event may be acute pallor of a limb due to an arterial embolism or spasm (14). Other clinical signs include hypotonia and poor feeding.

3. *Cerebral sino-venous thrombosis (CSVT)* is less common than PAIS, its incidence ranging between 2.6 to 12 per 100,000 neonates. Such thrombosis in full term neonates usually involves the superior sagittal or transverse sinuses and less frequently the medullary veins (15). Risk factors are similar as in PAIS. Neonates with CSVT usually do not require resuscitation. They may be initially considered healthy and sent to the maternity ward prior to present with non-specific symptoms such as apnoea, hypotonia, irritability, dehydration, or poor feeding. However, seizures are the most common sign, as approximately 50% of neonates with CSVT present with seizures within 48 hours of delivery (16).

Its pathophysiology is well understood in the context of Virchow's triad, i.e., stasis of blood flow, injury of the vessel wall and perturbation of the components of blood affecting clot formation and lysis. If a thrombosis in the cerebral venous system occurs, it impedes venous outflow, resulting in increased central venous pressure. As a result, intracranial hypertension can lead to cerebral ischaemia, which may lead to infarction, often haemorrhagic in nature. Imaging of the thrombus in the sino-venous system can be difficult (16). MRI and MR venography offer the most detailed and sensitive means to assess the clot. Management of neonatal CSVT is supportive with hydration, treatment of any underlying condition and anti-epileptic drugs (AEDs). For term neonates with CSVT and without significant intra-cranial haemorrhage, anticoagulation is the appropriate treatment (15).

4. *Intra-cranial haemorrhage* in term newborn infants may be spontaneous in nature, without identifiable risk factors such as birth trauma, vascular malformation, or coagulopathy. Rarely, intracranial haemorrhages are related to mutations in *COL-4a*, bleeding diathesis due to vitamin K deficiency, inherited thrombophilia, or infection. Often, a newborn will have more than one type or location of intra-cranial haemorrhage. Term neonates with intraventricular haemorrhage should be evaluated for co-existing CSVT (16). Isolated intraventricular haemorrhage is rarely associated with seizures unless it is large or associated with parenchymal haemorrhage (2). Parenchymal haemorrhage involving cortical or subcortical grey matter may cause seizure activity and reduced consciousness levels. Large haemorrhages can be detected with cerebral ultrasound, but MRI is the most reliable technique. Acute intra-cranial haemorrhage needs prompt neurosurgical consultation, but one should be aware that acute intervention might not always be indicated. On the other hand, many healthy neonates can have small subarachnoid or subdural haemorrhages due to delivery, without seizures or other clinical signs. When faced with seizure activity in a term infant, the presence of such small haemorrhages may explain the clinical seizures, but other potential causes must always be looked for (3).

5. *CNS infection* is an uncommon cause of symptomatic neonatal seizures (i.e. 5% of newborn seizures) (2). Usually, seizures from CNS infection also present with fever as well as multi-systemic disease. Lumbar puncture is recommended in all neonates with seizures and suspected infection (6). Bacterial infections are classically due to group B *Streptococcus* and *Escherichia coli.* Viral infections can be caused by herpes simplex virus, cytomegalovirus, enterovirus, parvovirus and even rotavirus. Seizures may present at any time during the neonatal period, occurring as late as at several weeks of age, e.g., late group B *streptococcal* or herpes simplex infection. Because of the ongoing inflammation, seizures resulting from CNS infections can persist longer than in ischaemic or brain injury. Consequently, these neonates should be monitored (EEG) for a longer period. Duration of therapy (AEDs) will depend on the result of the cultures of cerebrospinal fluid.

1. *Disturbances of electrolyte or glucose homeostasis* may cause acute seizures in the newborn infant as it likewise does in older children or adults. Treatment should be directed at determining and correcting the underlying aetiology of such abnormality. Conventional AEDs are usually ineffective and unnecessary as seizures promptly cease with correction of the underlying abnormality (7). It is important to stress that any metabolic disturbance (hyponatraemia, hypocalcaemia, and hypoglycaemia) that causes seizures deserves a thorough investigation to find the underlying pathology (e.g. profound hypocalcaemia can point towards a 22q11 mutation, hypoglycaemia can be caused by nesidioblastosis). Severe and long-lasting hypoglycaemia can cause occipital located cerebral damage as seen on the MRI (17). All newborns with suspected seizures should have a bedside glucose measurement, as well as laboratory testing for electrolyte disturbances.

6. *Neonatal abstinence syndrome* can occur in newborns who are chronically exposed to opioids in utero. During the acute phase, manifestations include poor feeding, gastro-intestinal disorders, abnormal sleep patterns and neurological signs such as jitteriness, irritability, crying, tremor, hypertonia and even seizures. Finnegan scores should be obtained during observation. Some non-epileptic manifestations, such as jerking movements during benign neonatal sleep myoclonus, may be mistaken for seizures. Of neonates with neonatal abstinence syndrome, only 7.5% manifest with seizures (18). EEG is thus mandatory for confirmation prior treatment.

B. *Early onset epilepsy*

About one in eight newborns with seizures has a neonatal-onset epilepsy. These syndromes may be associated with a brain malformation or a genetic abnormality. It is important to rapidly differentiate between neonatal epilepsy and symptomatic seizures, as these two entities require different investigations and treatment (3).

1. *The benign familial neonatal epilepsy* is the most common form and is linked with a *KCNQ2/KCNQ3* variant. Neonates have focal tonic sei-

zures but look healthy and have a normal inter-ictal EEG. There often is a family history of neonatal seizures.

2. *The benign idiopathic neonatal seizures* or fifth-day fits: newborns present convulsions around the fifth day of life; these seizures resolve within the first few weeks of life. There is no family history of epilepsy; an association with rotavirus has been suggested.

3. *Epilepsies associated with brain malformations* (cortical dysplasia, lissencephaly, megalencephaly) have a poor prognosis and encompass many syndromes. The newborn often presents with an abnormal neurological examination and feeding difficulties. The EEG shows significant background rhythm abnormalities in addition to seizures. Clinical seizures are often generalized and tonic; spasms can be associated.

4. *Neonatal epileptic encephalopathies* present during the first week of life in an encephalopathic child with crises that are refractory to AEDs. *KCNQ2* mutations are often involved. MRI is usually normal. Seizures are mainly tonic, and EEG is abnormal. The prognosis is poor.

5. *Epilepsy associated with inborn errors of metabolism* often presents with multifocal myoclonus, hypotonia and an abnormal EEG between seizures. This group is also called "early myoclonic epilepsy". Aetiologies include pyridoxine-dependent epilepsies, sulphite oxidase deficiency, nonketotic hyperglycinaemia, Menkes disease, Zellweger syndrome, etc.

Confirmation of seizure activity

Seventy percent of neonatal seizures are sub-clinical or subtle (10). They may be of short duration or very focal, making their diagnosis challenging. They may not be detected clinically unless the newborn is under direct observation by a trained caregiver at the time of the seizure (10). EEG monitoring as well as video recording in NS constitute essential tools to the clinician, to prevent underdiagnoses of real seizures or overtreatment of non-epileptic events (10). Indeed, as under- and overtreatment are both harmful, accurate diagnosis is imperative and any suspicion of a seizure activity in a neonate must be confirmed with an EEG (19,20). EEG recording before initiation of treatment is essential to confirm whether paroxysmal events are real seizures as well as to document their electrical characteristics. In case of NS, precise determination of the predominant seizure type(s) can point to a diagnosis (4). All seizure activity present within the newborn EEG must therefore be described in detail by a neurophysiologist (12).

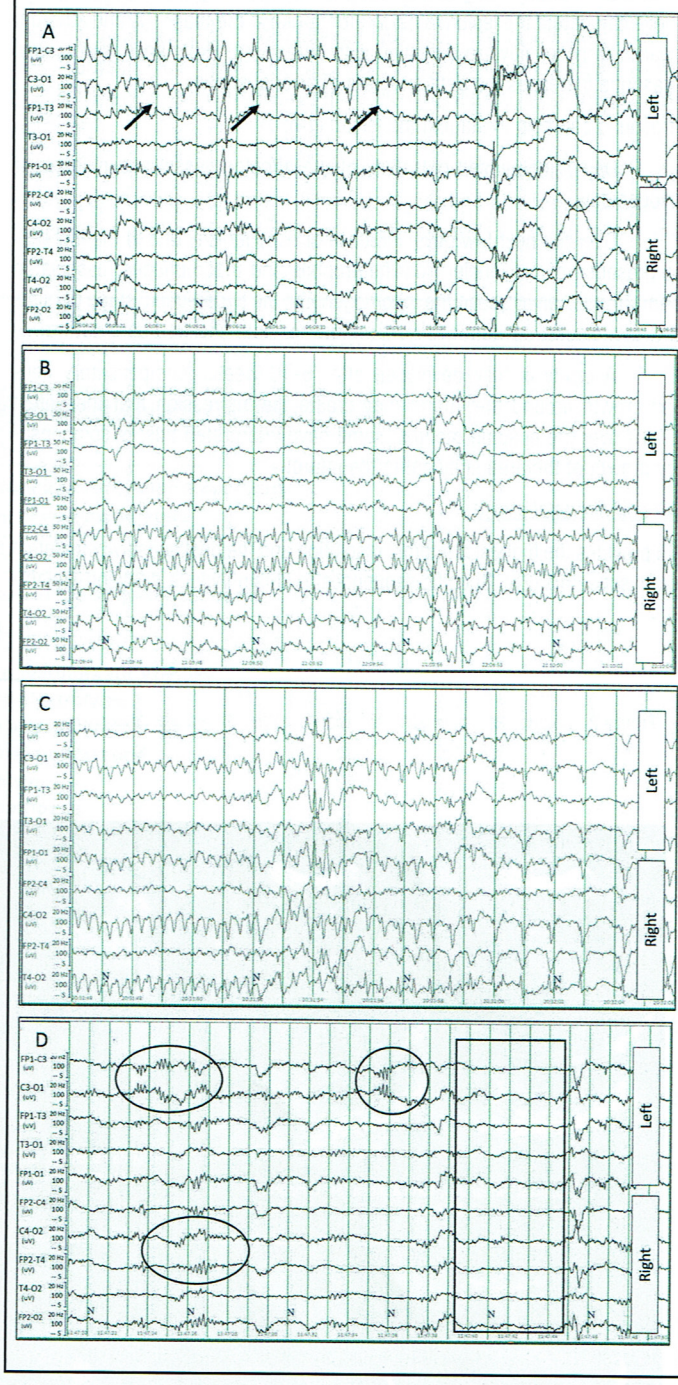
Technological advances have made EEG possible at the bedside within the incubator (21). Continuous video EEG with a conventional 10-20 montage modified for the newborn infant is considered as the gold standard (20,22). Full row EEG is a state-of-the-art technique, but its access might be difficult outside working hours. Amplitude-EEG (aEEG) can be a good alternative as it is easier to install and interpret. Nevertheless, as neonatal seizures are often of short duration (<1-2 min) and highly focal, they are often not detected by aEEG (7).

The EEG of neonates with symptomatic seizures presents in a wide variety of ways. Seizures are usually described as slow (1-3 Hz) discharges of rhythmic spikes or slow waves. The discharges are commonly localized, focal in nature, but they spread to the whole hemisphere or brain in 40% of cases (23). Change of morphology and frequency is common throughout the seizure, especially if the seizure propagates (23). Electrical crises are commonly of short duration (1 to 2 minutes) but they can be numerous, and their cumulative duration can evolve into a status epilepticus (24).

Distinctive EEG patterns according to the aetiology of the seizure activity have not been clearly described. Seizures arising from the midline vertex region are highly suggestive of CSVT (3). For PAIS, a set of non-specific observations has been noticed. Firstly, unilateral seizures are often observed on the hemisphere contra-lateral to the clinical manifestation. Secondly, the seizures are and remain focal in phase opposition on at the central region. Finally, the background rhythm between seizure activity in the affected hemisphere can be depressed, sometimes discontinuous and too rich with a rapid rhythm. (24). (Fig1)

When seizures are treated, conventional EEG monitoring should be continued up to 24 hours after resolution of the acute phase (20). Upon starting the

Figure 1 : *raw EEG from patients with arterial ischaemic stroke. A: focal ictal discharge on the left central lead (arrow); B: right unilateral ictal discharge; C: diffused ictal discharge evolving in frequency and morphology; D: discontinuous background pattern (rectangle) with excess of theta sharp waves (circles).*



treatment, continuous video EEG monitoring becomes even more relevant since some AEDs increase the proportion of electrical-only seizures (25). The use of AEDs may cause electro-clinical dissociation, a condition in which clinical symptoms cease to manifest, but electric seizures are still present (3). The contemporary association of aEEG gives an overview of the last hours of recording and can provide information on the crisis burden. Continuous video EEG and aEEG thus constitute unavoidable diagnostic and therapeutic tools for the acute neurologic neonatal patient.

Neuroradiographic investigations

Imaging findings are highly specific to differentiate focal infarction from haemorrhage, from asphyxia and from lesions due to hypoglycaemia or infection. Both cranial ultrasound and MRI are necessary for a full description of the patterns of injury. Examples of imaging findings are here summarized for focal brain injury, as the gradual improvement of imaging in the detection of stroke and other focal lesions stands as an example for neonatal brain imaging in general.

Ultrasound in arterial ischaemic stroke

PAIS can nearly always be visualized with ultrasound, except for small cortical infarcts far away from the transducer. It may however take several days before hyperechoic change is apparent beyond doubt. Even in cases of temporal or occipital infarction, targeted ultrasound from the temporal or posterior fontanelle can detect the lesion. A perforator stroke in the thalamus and striatum is particularly sensitive to detection with ultrasound. Experience with cranial ultrasound increases the detection rate of arterial stroke.

Ultrasound can help in staging the lesion (14):

- Day 1: decreased pulsatility of the affected vessel and mild hyper echogenicity.
- Over the next few days: increase of echogenicity due to the increasing presence of cell nuclei from neutrophils and macrophages; associated haemorrhage can increase the inhomogeneity; the hyperechoic stage persists for 3 to 4 weeks; cavitation follows an intermediate checkerboard pattern.
- A cavity is fully developed after 6-10 weeks; compensatory neuropil growth around the infarct may create the impression that the defect shrinks over the ensuing months; some have interpreted this as compensatory growth of the area adjacent to the infarct.

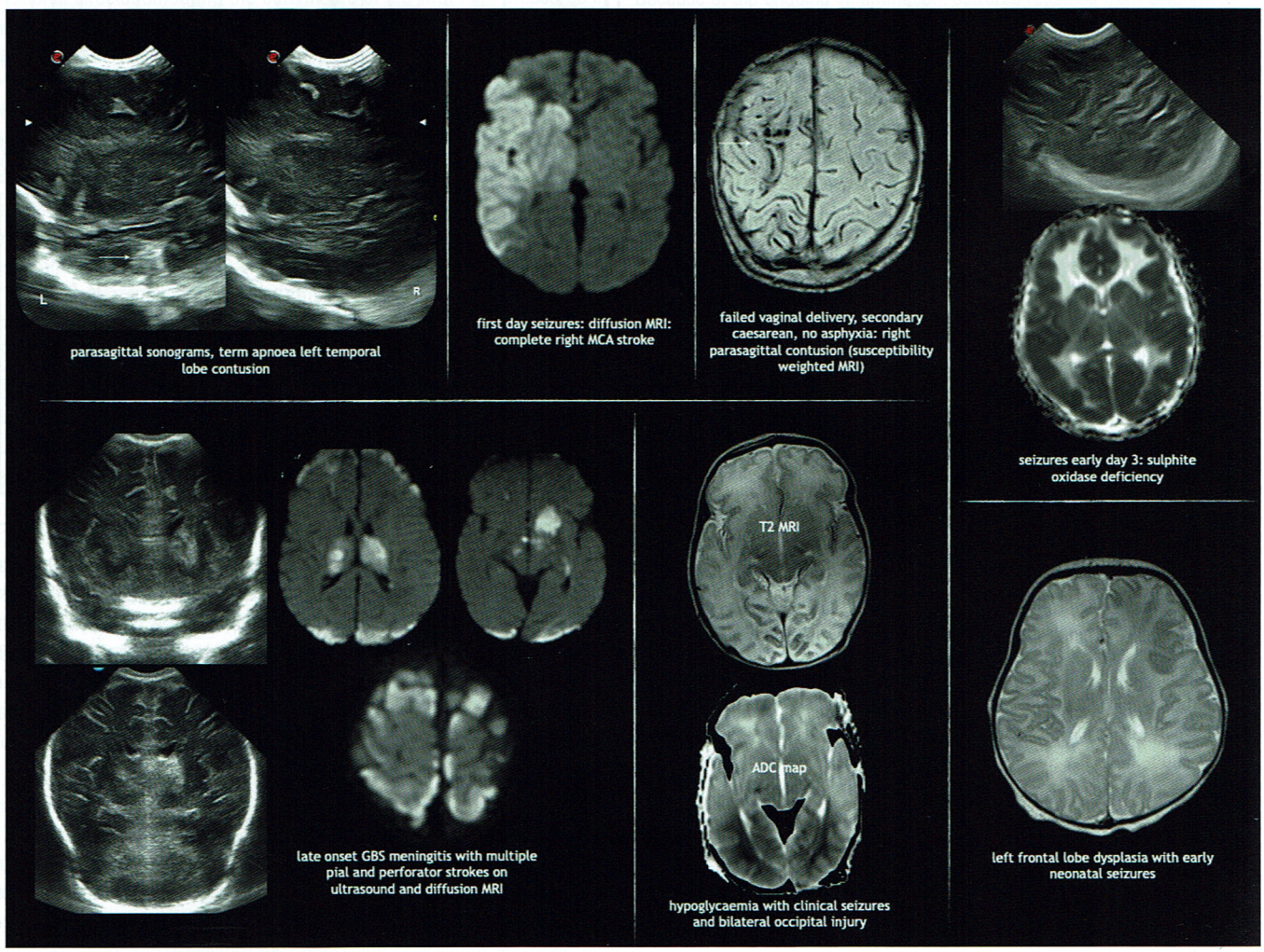
MRI and neonatal stroke

MRI provides the highest anatomic resolution and the best sensitivity to detect acute ischaemia (26). Specific sequences to obtain include diffusion-weighted imaging (from insult to about 7 days later), T1- and T2- weighted imaging, and susceptibility-weighted imaging. A MR angiography of the head and neck should be considered because it can easily be added to the initial MRI evaluation.

T2-weighted images in term infants with neonatal stroke demonstrate a high signal intensity in affected cortical grey matter and white matter during the first week of life, whereas T1-weighted imaging reveals a low signal intensity in the involved cortical grey matter. Between weeks 1-4 after birth, cortical grey matter signal intensity is high on T1- and low on T2-weighted imaging (i.e., cortical highlighting). Serial MRI confirms that in neonates with PAIS, the onset of injury is around the time of delivery. Tissue breakdown is maximal around 6 weeks. Three-site involvement of the hemisphere, the basal ganglia and the posterior limb of the internal capsule is strongly associated with later contralateral hemiplegia irrespective of the size of the infarct.

Diffusion-weighted imaging is used to depict cytotoxic oedema and provides image alterations within hours of the initial injury (27). Visualization of the lesion using diffusion-weighted imaging is best observed within the first 2-4 days from the moment of the initial injury. In the acute stage intensity changes are seen along the pyramidal tract. This phenomenon has a prognostic value especially at mesencephalic and pontine level and is referred to as pre-Wallerian degeneration. The extent of such acute corticospinal changes may predict the severity of the hemi-syndrome. Recruitment of ipsilateral tracts may predict maintenance of function in the affected limbs. Advanced post-acquisition quantification of diffusion tensor imaging data allows mapping of white matter connections, so called tractography. Tractography can refine subjective prediction of motor dysfunction.

Figure 2 : *Cerebral ultrasounds and MRI pictures related to neonatal seizures*



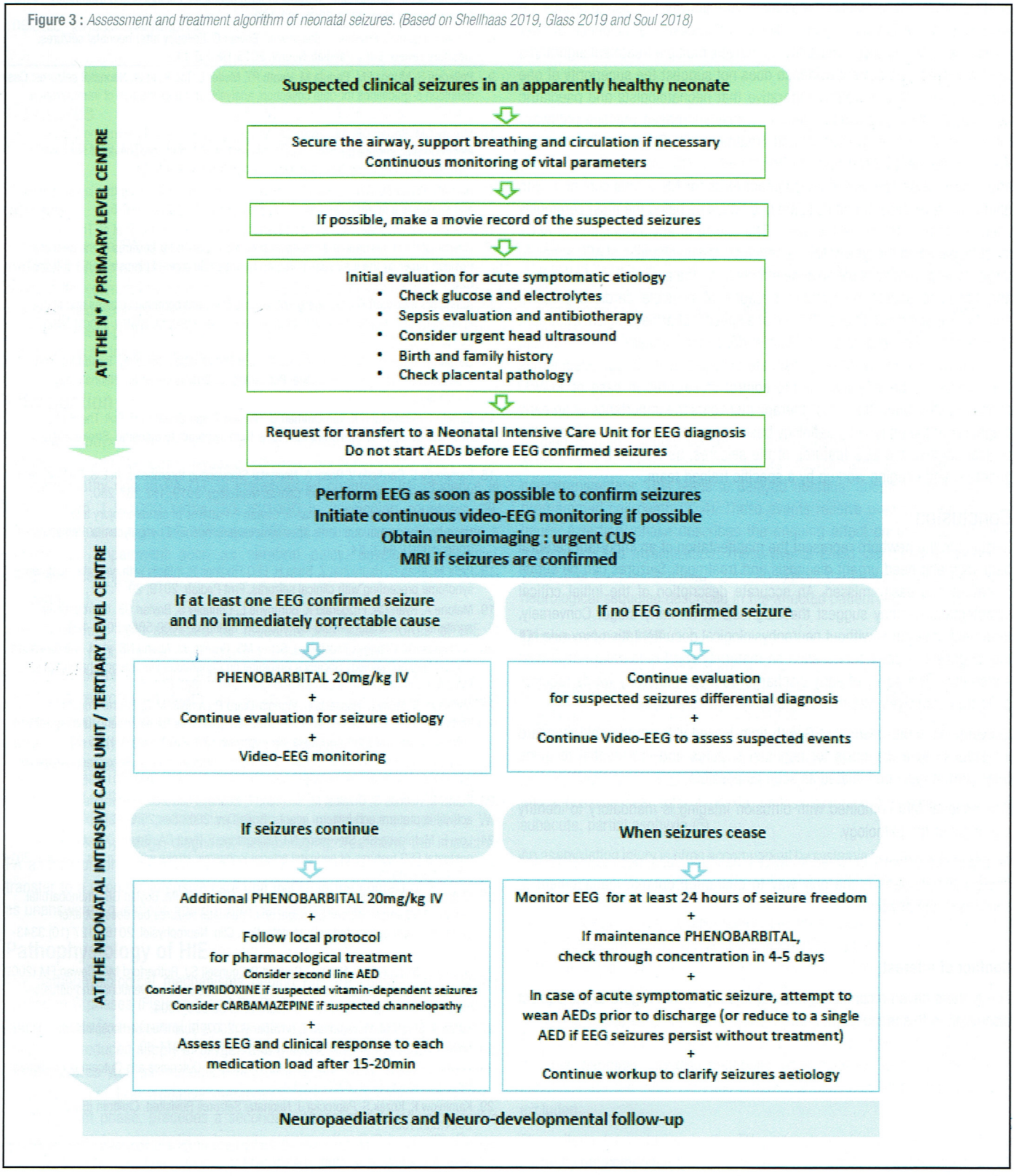
Treatment and algorithm of care in case of acute symptomatic seizures

Whilst being a rare neurological disorder, NS are associated with a high risk for severe brain lesions, epilepsy in childhood as well as cerebral palsy and cognitive impairment (28). Accurate recognition, appropriate diagnosis and early treatment are therefore of utmost importance (6). A protocol for the management of suspected NS is proposed in Figure 3.

The evaluation and treatment of a newborn infant with suspected seizures must occur simultaneously (6). As during any neurologic emergency, the first step involves accurate management of the airway, breathing and circulation. Priority should be given to the identification of easily correctable causes such as electrolyte disturbances or hypoglycaemia (3,29). If infection is suspected, cultures of blood, urine and cerebrospinal fluid should be obtained as soon as feasible, to promptly initiate antibiotics or antiviral medication (3). Every case of NS should be discussed with a tertiary level centre and transfer must be considered to provide cerebral monitoring using (video)-EEG, as well as accurate imaging to establish a diagnosis. In 2011, the American Clinical Neurophysiology Society (ACNS) developed specific guidelines on neonatal monitoring with conventional EEG (20). The guidelines state that electrophysiological monitoring must be proposed to every newborn with suspected seizures if correction of the underlying aetiology cannot be quickly obtained.

For high-risk neonates (e.g., with hypoxic-ischaemic encephalopathy or intra cranial haemorrhage) treatment with AEDs should be started immediately after suspected seizures, without waiting for EEG results (3,6,29). If the diagnosis

Figure 3 : *Assessment and treatment algorithm of neonatal seizures. (Based on Shellhaas 2019, Glass 2019 and Soul 2018)*



is unclear, treatment may be continued until EEG seizures are confirmed. Once seizures are recorded on EEG, prompt treatment is indicated (3,29).

Early treatment of NS with AEDs improves outcome (11). However, overtreatment may be harmful as side effects of AEDs may include hypotension, respiratory depression, and arrhythmia (11). Moreover, chronic use of AEDs is associated with cognitive and memory impairment in children (30). The decision to initiate AEDs therefore not only depends on the aetiology but also includes the seizure burden, i.e., the duration of electrographic seizures in a given period. A long seizure burden is associated with poor outcome (12). It is generally considered that rare and brief seizures may not require immediate treatment but require more prolonged EEG monitoring. A seizure burden higher than 30-60 seconds per hour is considered as a threshold to initiate treatment (22).

Discussion on treatment options is beyond the scope of this paper. The aim of AEDs is not only to resolve the acute seizure activity, but also to reduce the severity of acute brain injury and ideally to decrease the incidence of later epilepsy and/or neurologic disability (7). Hereto, multiple treatment algorithms exist worldwide, as current evidence does not suggest the superiority of one particular AED. It is therefore imperative that neonatologists and paediatric neurologists develop hospital-specific, consensus-based practice pathways for neonatal seizure evaluation and treatment (3). Phenobarbital remains the most frequently used first-line treatment for NS, but its efficacy is only about 50% (3,6). The use of concomitant AEDs for NS is thus common, with phenytoin, levetiracetam, midazolam and lidocaine being the most commonly used second- or third-line therapies. The choice of any association of AEDs must be based on the type of NS, its aetiology, the mechanism of AED action to target synergy and possible adverse effects (e.g., the association of phenytoin and lidocaine should be avoided because of possible cardio-depressive effects). For some conditions, the use of a specific pharmacological treatment is indicated. For example, in vitamin-dependent epilepsies one should consider pyridoxine, pyridoxal-phosphate or folinic acid. Carbamazepine has been shown to be effective for the control of seizures in case of *KCNQ2* channelopathy. Such "targeted" therapy highlights the importance of an early diagnosis of the underlying aetiology based on an appropriate analysis of the clinical context, the EEG features of the seizures, as well as the laboratory, genetics, and imaging workup by a specific trained team.

Conclusion

Seizures in the newborn represent the manifestation of an important cerebral pathology and need urgent diagnosis and treatment. Seizures can be subtle in nature and easily missed. An accurate description of the initial critical symptomatology may suggest the diagnosis at an early stage. Conversely, treatment of seizures without neurophysiological documentation may rule out the diagnosis. A good surveillance on maternity ward is therefore of utmost importance. The policy of early discharge from our maternity wards requires us to train midwives who monitor newborn infants at home.

Conventional multi-channel EEG with time-locked video is the gold standard in establishing a diagnosis for neonatal seizures and is essential to guide treatment. It must be initiated as soon as possible.

Conventional MRI combined with diffusion imaging is mandatory to identify the origin of the pathology.

An organised network between midwives, paediatricians, neonatologists, and neuro-paediatricians is the only way to guarantee optimal management of seizures in the newborn.

Conflict of interest

The authors have no conflict of interest to declare with regard to the subject discussed in this manuscript.

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