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Acute symptomatic seizures in term neonates: Etiologies and treatments

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A B S T R A C T

Acute symptomatic seizures caused by either diffuse or focal perinatal hypoxic–ischemic insults and intracranial hemorrhage in term newborns make up the large majority of all neonatal seizures. Acute seizures are one of the most common neurological disorders in term newborns who require admission to the neonatal intensive care unit. Despite elucidation of seizure pathogenesis in this population using animal models, treatment is limited by a lack of good evidence-based guidelines because of a paucity of rigorously conducted clinical trials or prospective studies in human newborns. A result of this knowledge gap is that management, particularly drug choice, is guided by clinical experience rather than by data informing drug efficacy and safety. This review summarizes the common etiologies and pathogenesis of acute symptomatic seizures, and the current data informing their treatment, including potential novel drugs, together with a suggested treatment algorithm.

1. Introduction

Acute symptomatic neonatal seizures represent the majority of neonatal seizures, and are one of the most common neurological disorders in term newborns admitted to the neonatal intensive care unit (NICU). The three most common etiologies of neonatal seizures are all acute neurologic disorders, namely the ischemic/hemorrhagic brain disorders of hypoxic–ischemic encephalopathy (HIE; 38%), ischemic stroke (18%), and intracranial hemorrhage (12%) [1]. Other etiologies of acute symptomatic neonatal seizures include transient metabolic derangements (4%) and central nervous system (CNS) infections (4%). The proportion of seizures caused by these etiologies has not changed much in the last decade [2], although acute meningitis and/or encephalitis are much less common in developed countries now compared with earlier decades. Currently, acute CNS infections are a relatively uncommon cause of neonatal seizures, on par with many other congenital causes, such as brain malformations (4%), inborn metabolic disorders (3%), and other genetic causes of benign (3%) or severe neonatal onset epilepsies (6%). Additionally, the proportion of neonatal seizures caused by ischemic/hemorrhagic brain injury is probably higher than the numbers cited above, given that these data were derived from a study of tertiary/quaternary NICUs where there is likely a higher proportion of newborns with congenital etiologies of seizures or epilepsy, such as brain malformations, inborn errors of metabolism and genetic epilepsies. This review will focus on the etiologies, pathogenesis and management of acute symptomatic seizures in term newborns, related to acute acquired rather than congenital disorders.

2. Diagnosis of acute symptomatic seizures

Acute symptomatic seizures in newborns can have a subtle, clonic, myoclonic, or less commonly tonic semiology, depending which brain region(s) is/are involved in the seizure activity, or the seizures may be entirely subclinical. Even when clinically evident, brief seizures without change in vital signs may not be detected by a caregiver or medical provider unless the newborn is under direct observation at the time of the seizure [3]. Additionally, many paroxysmal behaviors in newborns are not seizures, so clinical assessment of seizures may result in both over- and underdiagnosis [3]. Thus the diagnosis of seizures in newborns requires electroencephalography (EEG), ideally continuous video-EEG with a conventional 10–20 montage modified for neonates [4]. A recent large cohort study showed that 62% of all newborns with seizures had at least one subclinical seizure and 16% of newborns had only

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subclinical seizures [1]. Subclinical seizures are also more likely to occur in the setting of severe encephalopathy and administration of antiseizure or sedative medications, and clearly if paralytic medications are administered. Neonatal seizures are often of short duration (<1–2 min), and are highly focal with very little spread to other brain regions, thus are often not detected by one- or two-channel amplitude-integrated (a)EEG monitoring [5]. Full montage video-EEG is needed to detect very brief and/or focal seizures [5], and video is needed to distinguish frequent EEG artifacts from movement or routine care that may be mistaken for seizure. Finally, continuous video-EEG monitoring (cvEEG) is required to determine the effect of antiseizure medications, since some medications increase the chance of subclinical seizures or less clinically evident seizures (e.g., seizures may be briefer or more focal with treatment) [6,7], and will lead to the false conclusion that the medication has been effective.

Several historical and clinical characteristics of seizures help point towards a specific etiology. Timing of seizure onset provides the first clue regarding seizure etiology, as seizures caused by HIE often present in the first 12–24 h after birth, whereas seizures resulting from perinatal stroke, hemorrhage or infection often have later onset [8], with some infections presenting with seizures weeks after birth. Seizure type and location are also suggestive of the underlying etiology. Focal clonic seizures that are unilateral often point to a focal ischemic stroke or hemorrhage, whereas multiple different semiologies and/or locations of seizures point to diffuse processes such as HIE, metabolic disorder or CNS infection, or multifocal stroke or hemorrhage. Interestingly, a large cohort study showed that seizure burden was not appreciably different among the three ischemic/hemorrhagic etiologies of acute symptomatic seizures [1].

3. Hypoxic–ischemic encephalopathy

The most common and important cause of acute symptomatic neonatal seizures is hypoxic–ischemic encephalopathy (HIE) [1]. Its importance relates not only to HIE being the most common etiology, but to the emergent detection and treatment of HIE with therapeutic hypothermia to reduce mortality and neurologic morbidity, and the increasing evidence that the acute seizures occurring in ~25–50% exacerbate the perinatal brain injury. The evidence that seizures exacerbate ischemic brain injury is more readily derived from animal models [9], but there is also supportive evidence from human studies [10–12]. Another common feature of HIE is the frequent occurrence of subclinical seizures, in addition to the usual clinical seizure semiologies that can occur in newborns (subtle, clonic, myoclonic, tonic). While there remains some debate about the utility of treating electrographic-only seizures, current evidence points to a harmful effect and a potential benefit of treatment of subclinical seizures on long-term neurologic outcome [11]. This notion that improved detection and treatment of electrographic as well as electroclinical seizures may improve outcome underlies the current emphasis to use continuous video-EEG monitoring (cvEEG) with a full neonatal EEG montage to both detect seizures in newborns with HIE (or encephalopathy of unclear etiology), and to improve treatment of acute symptomatic seizures. Thus the current American Clinical Neurophysiology Society guideline supports a minimum of 24 h of cvEEG for all newborns with encephalopathy and/or suspected seizures for adequate detection of seizures [4] (discussed by Katsarou et al. in this issue). The duration of cvEEG monitoring for suspected HIE varies among institutions, as, although seizures often have onset within 6–12 h of birth, there are instances of seizure onset occurring as late as 36 h, or rarely, new onset or recurrence of seizures during rewarming after therapeutic hypothermia [1].

4. Stroke

Perinatal stroke is the second most common cause of symptomatic seizures in newborns. Although focal ischemic stroke has similarities with the diffuse ischemia of HIE, there are a few important differences. Seizures caused by focal stroke often present at an older age than they do for HIE, up to 24–48 h after birth or older. Since the middle cerebral artery territory is most commonly affected [13], newborns often present with focal clonic seizures, presumably emanating from the injured motor cortex. Seizures may have focal sharp waves/spike–polyspikes with frequency of 1–2 Hz and phase reversal over the central region. Perinatal stroke may be hemorrhagic, whether venous or arterial in origin, but hemorrhage is more common with venous infarction [14]. Hemorrhagic transformation of perinatal arterial stroke is uncommon, occurring in <15% of all neonatal arterial stroke in the largest report, which includes neonates with congenital heart disease or other underlying conditions [13].

5. Intracranial hemorrhage

Almost all types of intracranial hemorrhage (ICH) can be associated with seizures, depending on location and size [2]. Often, a newborn will have more than one type or location of ICH, with seizures resulting from one or more of the different hemorrhages or locations of ICH. Epidural hemorrhage is rare in newborns, and associated seizures may reflect other injury, whether from other ICH or ischemic brain injury [15]. Parturitional subdural hemorrhage (SDH) in the posterior fossa, typically posterior to the cerebellum and/or lining the tentorium, is probably the most common type of ICH, does not cause seizures, and has been documented to occur in asymptomatic newborns [16]. In contrast, seizures related to SDH in the anterior and middle cranial fossae may be related to associated subarachnoid hemorrhage (SAH), although large supratentorial SDH with cerebral compression can result in seizures. Subpial hemorrhage, a subtype of SAH that often causes seizures, is most often related to trauma with contusion or from venous compression or obstruction and is most often found in the temporal lobe [17]. Unsurprisingly, cerebral parenchymal hemorrhage involving cortical or subcortical gray matter commonly causes seizures. The cause of parenchymal hemorrhage may not be identified, even with magnetic resonance angiography or venography, and may sometimes be related to rupture of underlying vascular malformations. Thalamic hemorrhage is often a venous hemorrhagic infarction with associated intraventricular hemorrhage, which may be the consequence of thrombosis in the internal cerebral veins or more diffuse sinus venous thrombosis [14,18]. Isolated intraventricular hemorrhage (IVH) is rarely associated with seizures unless the IVH is large, but IVH with seizures is most often associated with parenchymal brain injury, whether ischemic or hemorrhagic, and may occur in the setting of perinatal asphyxia and HIE [1,19]. Since cranial ultrasound (CUS) can detect most types of ICH, and almost always detects large ICH that requires surgical intervention, obtaining an early CUS in newborns with seizures is a useful step in diagnostic testing, when magnetic resonance imaging cannot be obtained quickly.

6. Metabolic disorders and derangements

Transient disturbances in electrolytes may result in acute seizures in newborns, as can occur in older children and adults [1]. For example, hyponatremia and hypocalcemia can result in acute seizures in the first days after birth. In these cases, treatment is directed at determining the cause and correcting the underlying etiology of the electrolyte or metabolic derangement, as

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