Clinical and neurophysiologic correlates of neonatal seizures

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SEIZURES pose a number of problems in the care of newborn infants. Seizure hazard is greater in the neonatal period than at any other time. In addition, clinical seizures are the most frequent sign—and indeed may be the only sign—of central nervous system (CNS) disorder in the neonate. Clinical seizures, however, may be difficult to recognize, and if untreated, may further compromise an already injured developing brain. Conventional anticonvulsant therapy, on the other hand, may not be completely effective in eliminating seizures, and overtreatment with large doses of anticonvulsants may also have adverse effects on the immature brain.

To address these problems of diagnosis and management effectively, it is essential that clinical seizures be recognized and distinguished from other behaviors that are not seizures. In clinical practice, however, most abnormal, stereotypic behaviors of the neonate are considered to be seizures and presumed to be epileptic in origin. Utilizing cribside electroencephalographic (EEG)/polygraphic/video monitoring, we have recently evaluated this concept and the assumption that all neonatal seizures are initiated and mediated by the same pathophysiological mechanism.[1]

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CLINICAL MANIFESTATIONS OF NEONATAL SEIZURES

The clinical features of neonatal seizures have been characterized by others over the past several years. Most notable are several French investigators[2–6] who, beginning in the 1950s, described almost all the clinical manifestations currently considered to be seizures. Motor phenomena were characterized as either generalized tonic or focal or multifocal clonic. Clonic seizures could be bilateral but occur asynchronously on two sides of the body. It was appreciated that generalized tonic-clonic seizures do not occur in neonates.

Clinical behaviors that have since become known as "subtle" seizures were also described in this early period of investigation. Eye opening, paroxysmal blinking, nystagmus, chewing, rowing, and pedaling movements were described by Minkowski and Sainte-Anne-Dargassies.[3] Dreyfus-Brisac and Monod[7] remarked on the "atypical and anarchic" character of neonatal seizures and their propensity for only slight "peripheral phenomena." The autonomic features of some types of seizures were also described, including vasomotor changes, changes in respiration and skin color, and salivation.

Later, beginning in 1973, Volpe[8,9] classified neonatal seizures according to clinical manifestations: focal clonic, multifocal clonic, tonic, myoclonic, and subtle seizures. The last term comprised seizures with ocular movements; oral-buccal-lingual movements; swimming, pedaling, or rowing movements; or autonomic signs. This is currently the most widely accepted classification system.

EEG AND NEONATAL SEIZURES

The interpretation of the neonatal EEG in relation to clinical diagnosis and management may be difficult. The interictal EEG provides few, if any, reliable signs of potential epileptogenesis. In the neonate, interictal sharp waves may be normal, of questionable significance, or clearly abnormal.[10] If abnormal, however, they are most often nonspecific and are usually not indicative of an epileptic process. Epileptogenesis in the neonate, as expresssed by the EEG, has been described as an "all-or-nothing" process; a single epileptiform discharge will initiate an electrographic seizure.[11]

The electrographic patterns of seizures are highly variable. They may be localized in a circumscribed region of the brain or may spread rapidly. They may be brief but have the potential to be quite prolonged. The seizure discharges themselves may also be highly variable in morphology, amplitude, and duration.[10,12]

EEG/polygraphic/video monitoring

The early characterizations of neonatal seizures and their currently accepted classification formed the basis for our recent investigations.[1,13,14] We utilized cribside EEG/polygraphic/video monitoring techniques to study neonates suspected of having seizures.[1,13,15] We analyzed the video recordings for clinical events currently considered to be seizures and determined their relationship to simultaneously recorded EEG seizure activity. We also observed the way the seizures responded when tactile stimulation and restraint were used, and identified the etiologic factors and short-term outcome of the seizures. The methodology and specific results of these studies have been described elsewhere.[1,13,14]

During our monitoring studies of neonates, we were able to record all the clinical behaviors currently considered to be seizures. Although all clinical events were abnormal, not all were closely associated with EEG seizure activity. Some of the behaviors, in fact, occurred in the absence of any such activity. Based on the clinical characteristics of the seizures and their relationship to EEG seizure activity, an electroclinical classification of neonatal seizures was devised (see *Tables 1* and *2*).

TABLE 1
ELECTROCLINICAL CLASSIFICATION OF NEONATAL SEIZURES (n = 100)

Type of seizure	Number and % of infants
Clinical seizures with a consistent electrocortical signature	33
Clinical seizures without a consistent electrocortical signature	60
Electrical seizures without clinical seizures	5
Infantile spasms	2

From Kellaway and Mizrahi.[14]

TABLE 2
CLASSIFICATION OF CLINICAL SEIZURES (n = 95)

Type	Number	%
Clinical seizures with a consistent electrocortical signature	33	34.7
Focal clonic: unifocal, multifocal, hemiconvulsive, axial	23	24.2
Focal tonic: asymmetric truncal, eye deviation	5	5.2
Myoclonic: generalized, focal	4	4.2
Apnea*	1	1.1
Clinical seizures without a consistent electrocortical signature	60	63.2
Myoclonic: generalized, focal, fragmentary	17	17.9
Generalized tonic: extensor, flexor, mixed extensor/flexor	14	14.7
Motor automatisms: oral-buccal-lingual, ocular signs, progression movements, complex purposeless movements	29	30.5
Infantile spasms	2	2.1

* Apnea occurred in one infant treated with phenobarbital prior to monitoring
From Kellaway and Mizrahi.[14]

CHARACTERIZATION AND CLASSIFICATION OF NEONATAL SEIZURES

Clinical seizures with a consistent electrocortical signature

These clinical seizures always occur in a time-synchronized relationship to EEG seizure activity and include focal clonic, focal tonic, and some myoclonic seizures. Focal clonic seizures consist of rhythmic twitching of facial, limb, or axial muscles. They may be unifocal, multifocal, hemiconvulsive, or axial. Focal tonic seizures are a sustained asymmetric posturing of the limbs or trunk or a sustained deviation of the eyes. Myoclonic seizures with a consistent electrical signature may occur as either generalized or focal jerks of distal or proximal (axial) muscle groups.

In our studies, neonates with focal clonic seizures were usually awake and alert between seizures, and

their interictal background EEG activity was usually normal. Focal clonic seizures were most often associated with focal structural lesions, subarachnoid hemorrhage, infection, or (more rarely) metabolic disorders. The neonates with focal clonic seizures usually had a good short-term prognosis.

Clinical seizures without a consistent electrocortical signature

Clinical seizures may also occur either without any accompanying EEG seizure activity or with an inconsistent relationship to such activity if it is present. This category includes some myoclonic seizures, all generalized tonic seizures, and motor automatisms.

Myoclonic seizures unassociated with EEG seizure activity may be either generalized or focal. Bilaterally symmetric tonic seizures are extensor, flexor, or mixed extensor/flexor. Motor automatisms (classified as subtle seizures by Volpe[9]) include oral-buccal-lingual movements (puckering, sucking, grimacing, or tongue protrusion), ocular signs (eye opening, blinking, oscillatory or roving eye movements), progression movements (swimming or rotary arm movements, stepping or pedaling of the legs), and complex purposeless movements.

Neonates who had generalized tonic seizures, motor automatisms, or myoclonic seizures unassociated with EEG seizure activity were characteristically obtunded or comatose, and their background EEG activity was abnormal (either depressed and undifferentiated or not of cerebral origin). These types of seizures were most often associated with hypoxic-ischemic encephalopathy and a poor short-term outcome.

In infants with generalized tonic posturing or motor automatisms, tactile stimulation provoked behaviors identical to those observed spontaneously. Both provoked and spontaneous behaviors could be suppressed with restraint or repositioning of the trunk or extremities.

Electrical seizures without accompanying clinical seizures

Electrical seizures without clinical signs may occur in two circumstances. First, they may occur in infants not treated with anticonvulsants who are obtunded or comatose and who have depressed and undifferentiated background EEG activity. The electrical seizures are usually of the "depressed-brain type"[10] and the discharges are low in amplitude, remain confined to circumscribed regions, and show little augmentation.

Second, electrical seizures may occur in the absence of clinical seizures when the two become "decoupled" by anticonvulsant therapy. Infants who have focal clonic or focal tonic seizures accompanied by electrical seizure activity before anticonvulsant treatment may show persisting electrical seizures when the clinical seizures have stopped after administration of anticonvulsants. This control of the clinical seizures with persisting electrical seizure activity has been termed "decoupling."[1]

Mixed seizures

Although most infants have only one type of seizure, some may have more than one. The usual combinations are motor automatisms, tonic posturing, and some myoclonic seizures, but some infants may have focal clonic seizures and tonic posturing and/or automatisms.

NEUROANATOMIC AND NEUROPHYSIOLOGIC DETERMINANTS OF NEONATAL SEIZURES

On the basis of our monitoring studies, we have proposed that at least two pathophysiologic mechanisms may be responsible for initiation and mediation of the different types of neonatal seizures.[1,11,13] An epileptic process is responsible for focal clonic and focal tonic seizures. In addition, we hypothesize that a nonepileptic process may be responsible for tonic posturing and motor automatisms.

Epileptic pathophysiology

The well-localized and, at times, fragmentary or anarchic character of some neonatal seizures is thought to be dependent on the relative epileptogenicity of brain structures and the properties of the brain that determine the propagation of electrical seizure activity in the developing brain.

Animal investigations indicate that the hippocampus, compared with the neocortex, has a greater structural complexity and exhibits increased excitability.[16] There is, however, a prominence of inhibitory synaptic activity in the immature neural network,[17] and the degree of development of the cytoarchitecture and myelinated pathways may prevent or delay the cortical spread of seizure activity.[6,18–20] These properties of the immature brain, which tend to confine rather than spread electrical activity, may restrict the epileptic discharges to the specific brain regions from which they originate.

Features that tend to confine epileptic electrical

activity may account for the clinical manifestations of some types of neonatal seizures. Focal clonic and focal tonic seizures may involve well-circumscribed regions of the body, just as epileptic discharges arise and remain localized within a specific, well-localized brain region.

The relative excitability of the hippocampus compared with neocortical inhibition may account for features of other types of seizures (not well characterized in our current studies) that have a predominance of signs mediated by the autonomic nervous system. These include changes in heart rate and blood pressure, pallor, flushing, pupillary dilatation or constriction, and salivation. These clinical signs may be mediated by activation of limbic system structures and may be initiated by epileptic activity within the hippocampus. The neurophysiologic characteristics of the immature brain suggest that there is a relative vulnerability of the hippocampus and that abnormal electrical activity tends to be confined to hippocampal structures, which may result in clinical seizures with a predominance of autonomic features.

Nonepileptic pathophysiology

Tonic posturing and motor automatisms do not require electrocortical seizure activity for their elaboration. The seizures may be epileptic in character but are generated in the brain stem without manifestation of paroxysmal epileptic activity at the scalp. An alternative explanation may be that the seizures are generated at a brain stem level by a nonepileptic mechanism. This explanation is based on clinical and electrographic findings as well as on response to stimulation and restraint.

Infants with generalized tonic seizures and motor automatisms have clinical and electrographic evidence of forebrain depression; they are obtunded or comatose and their background EEG activity is depressed and undifferentiated. Clinical events, identical to those occurring spontaneously, may be provoked by tactile or proprioceptive stimulation. Increasing the intensity of the stimulation at a single site, or constant stimulation at an increasing number of sites, results in an increase in the intensity of the behavior (*temporal* and *spatial summation*). There may also be spread of the response (*irradiation*) to other muscle groups. In addition, both spontaneous and provoked responses may be suppressed by restraint or repositioning of the affected limb or trunk. All of these features are characteristic of reflex behavior, as demonstrated by animal studies,[21–25] and not of epileptic mechanisms.

On the basis of these observations, we have proposed that tonic posturing and motor automatisms occur as a consequence of depression or absence of cortical tonic inhibitory influences on brain stem facilitory centers.[1,11,13] This results in a facilitation, or "release," of primitive brain stem and spinal motor mechanisms. It has been proposed that these behaviors be classified as "brain stem release phenomena" rather than as epileptic seizures.[11]

THERAPY

A detailed discussion of the use of anticonvulsants in neonates is provided by Painter (see article in this volume). Therefore, only two specific issues concerning therapy will be considered here. First, if some neonatal seizures are not epileptic in origin, anticonvulsant therapy may not be appropriate for all types of seizures. Clinical seizures with a consistent electrocortical signature are most clearly of epileptic origin; they include focal clonic and focal tonic seizures. Identification of these seizure types by EEG/polygraphic/video monitoring should suggest institution of anticonvulsant therapy. On the other hand, seizures that occur without accompanying EEG seizure activity and presumably are of nonepileptic origin may not require anticonvulsants.

It may be difficult to determine the effectiveness of anticonvulsant treatment of epileptic seizures. As noted above, when a drug such as phenobarbital, for example, is given to infants whose clinical seizures are closely associated with EEG seizure activity, the clinical seizures may stop while the electrical seizures persist virtually unchanged. Thus, the clinical seizures are decoupled from the electrical seizures.[1] The electrical seizures may be difficult to control, even when high dosages of anticonvulsants are used. However, the goal of anticonvulsant therapy for neonatal seizures has not been established: is it cessation of electrical seizures or of clinical seizures?

HETEROGENEITY OF NEONATAL SEIZURES

In the past, neonatal seizures have been characterized and classified according to clinical manifestations, but their clinical significance, pathophysiology, and therapy have been determined by considering all types of seizures as a single group.

Our monitoring studies suggest that various seizure types are associated with varying degrees of cerebral

injury and differing etiologic factors and short-term outcomes. In addition, it may be that not all neonatal seizures are initiated and mediated by an epileptic process; some may be the manifestation of primitive reflexes mediated by the brain stem in the presence of forebrain depression. Anticonvulsant therapy may not be appropriate for all types of neonatal seizures. Thus, exact characterization and classification of each type of seizure form the basis for accurate diagnosis, management, and prognosis of neonates with seizures.

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