



## Review

# Current Overview of Neonatal Convulsions

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### Abstract

Neonatal convulsions are one of the most common emergency neurological events in the early period after birth. The frequency has been reported to be 1.5 to 3 in 1000 live births. It has been established that the convulsion threshold is lower in infants due to immature neonatal neurons and differences in neurotransmitters. Hypoxic ischemic encephalopathy is the most common etiology in neonatal convulsions. Other causes vary, and may be related to the level of development of the country. Convulsions are classified into 4 different types according to the clinical findings. The most common is the subtle (undefined) type of seizure; the other types are defined as clonic, tonic, and myoclonic seizures. Non-epileptic paroxysmal movements frequently seen in the neonatal period, should not be confused with seizures. The most common non-epileptic paroxysmal movements are jitteriness, benign neonatal sleep myoclonus, and hyperekplexia. A newborn that experiences convulsions should be hospitalized and monitored with continuous video electroencephalogram, if possible. If an initial rapid evaluation detects an acute metabolic disorder, treatment is provided, and, if warranted, it will be followed by a plan for further treatment with anticonvulsant drugs. Phenobarbital is still currently recommended as first-line therapy, though there are studies of other anticonvulsant drugs. Levetiracetam and phenytoin are commonly used as second-step anticonvulsant drugs. The aim of treatment should be not only to stop acute symptomatic seizures, but also to reduce the risk of brain damage and to minimize the possible negative effects of epilepsy and neurological deficits.

**Keywords:** Convulsion; newborn; phenobarbital.

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Neonatal convulsions are one of the most common emergency neurological diseases in the neonatal period. Since the potential adverse effects of convulsions on the brain are known, they must be treated urgently. In recent years, many studies have examined the use of anticonvulsant drugs in the newborn period; however, there is currently no standardized treatment protocol for neonatal convulsion management.

A convulsion is defined as a transient change in neurological function caused by a sudden, paroxysmal depolarization of a group of neurons. In cases of convulsions seen in the neonatal period, it is important to consider the seriousness of potential underlying diseases, the treatments that might be applied targeted at the etiology, and to remember that repetitive convulsions may have a permanent effect on the brain.<sup>[1, 2]</sup>

The frequency of neonatal convulsion has been reported to be 1.5 to 3 in 1000 live births.<sup>[3]</sup>

### Pathophysiology

Neonates have immature neurons and differences in neurotransmitter levels make them susceptible to seizures.<sup>[4]</sup> Immature neurons contain a larger number of excitatory N-methyl-D-aspartate and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid (AMPA) receptors, and fewer gamma-aminobutyric acid (GABA) receptors, which is one of the reasons for a low convulsion threshold in neonates. In addition, unlike in adults, GABAA receptors in neonates work as excitators through sodium-potassium-chloride cotransporter 1 (NKCC1), which also contributes to a low convulsion threshold.<sup>[5]</sup> (Fig. 1) In addition, in cases of hypoxia, the NKCC1 channel is upregulated and the convulsion threshold is decreased even more.

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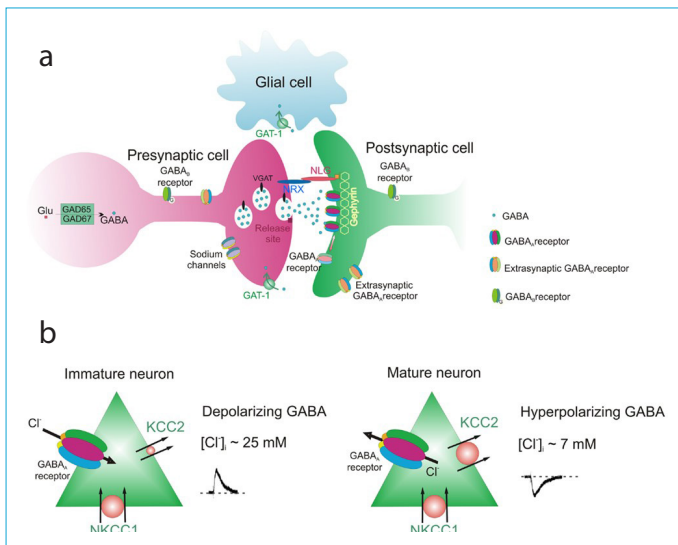
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**Figure 1.** Ion channels in the neurons of newborns and the role of neurotransmitters.

## Etiology

Hypoxic ischemic encephalopathy (HIE) is the most frequently detected cause of convulsion in the neonatal period (38%). Other known etiological factors include ischemic stroke (18%), intracranial hemorrhage (12%), epilepsy (6%), central nervous system infection (4%), and transient metabolic disorders (4%), whereas in 9% of the patients, no underlying etiology can be detected.<sup>[6]</sup> Differences in etiology have been observed according to the level of national development. There are studies reporting infection as the most common cause after HIE in developing countries.<sup>[7]</sup>

## Types of Convulsions

According to clinical findings, 4 types of seizures may be observed in the neonatal period: subtle, clonic, tonic, and myoclonic seizures.

**Subtle (unspecified) seizure** is the most common type of convulsion. It includes movements such as a tremor in the eyelids; a fixed gaze in the eyes or horizontal deviation; smacking, chewing, or other oral movements; and pedaling gestures. Autonomic findings such as tachycardia and hypotension often accompany these findings.

**Clonic seizure** is defined as rhythmic contractions occurring 1 to 3 times per second in any part of the body. The spasms may be focal, localized to a region of the body, or multifocal, and involve several parts of the body. It is usually not accompanied by a loss of consciousness. This type of seizure can be seen in cortical dysplasia and metabolic disorders. Electroencephalography (EEG) is usually used to detect pathological findings.<sup>[8, 9]</sup>

**Tonic seizure** may be focal or generalized, and is usually characterized by a sudden increase in tone in the muscle groups lasting less than one minute. Asymmetric tonic posturing is typically seen in the trunk or neck with continuous flexion or extension of an extremity. It is often seen in cases of intraventricular hemorrhage and hypoxic ischemic brain injury. The focal type of seizure usually manifests EEG findings, however no generalized pattern has yet been established.<sup>[8]</sup>

**Myoclonic seizure** may be focal or generalized. Focal myoclonic movements appear in the form of rapid isolated contractions in the head or an extremity. In generalized myoclonic seizures, contractions occur at the same time in both the arms and legs. It is differentiated from clonic seizures by the fact that it is typically shorter in duration, has no slow phase, and may selectively involve flexor muscle groups. Some myoclonic seizures may have pathological EEG findings.

## Non-epileptic Paroxysmal Movements

It is important to distinguish non-epileptic paroxysmal movements that are frequently seen in the neonatal period from seizures. The most common non-epileptic paroxysmal movements in early period after birth are defined as jitteriness, sleep myoclonus, and hyperflexia.

**Jitteriness** is the most common type of non-epileptic paroxysmal movement. It is characterized by quick, symmetrical vibrations that are not accompanied by autonomic findings. When the limb is passively flexed, contractions can be stopped. There is typically no need for any additional treatment for infants diagnosed with jitteriness.

**Sleep myoclonia** consists of fragmented myoclonic spikes observed during the rapid eye movement period of sleep. Typically, it stops when the infant awakens and does not cause any change in general condition. Infants diagnosed with sleep myoclonia generally do not require treatment.

**Hyperreflexia** is defined as hypertension and a very exaggerated startle response triggered by auditory, visual, or tactile stimulation. It occurs as a result of a mutation in the  $\alpha$  subunit of the glycine receptor and it can be autosomal dominant. Jitteriness and sleep myoclonia do not require treatment; however in hyperreflexia, due to the risk of apnea, aspiration, or sudden infant death syndrome, the initiation of clonazepam treatment and home monitoring with an apnea monitor is recommended.<sup>[10, 11]</sup>

## Diagnosis

A detailed history is very important in order to clarify the etiology when evaluating infants with seizures. A maternal infection in the prenatal period, congenital infections, diabetes, hypoglycemia, and a history of difficult birth are key

indicators of potential perinatal asphyxia. The characteristics of other individuals in the family should be examined for familial epileptic syndromes.

The physical examination findings are helpful in determining the etiology. For example, an atypical facial appearance may be a clue for many diseases, from various syndromes to central nervous system malformations and metabolic diseases. An abnormal smell in the sweat or urine can also be important for the diagnosis of metabolic diseases. Hemangiomas and skin spots, such as café au lait spots, on the body are significant signs for neurocutaneous syndromes. Following a physical evaluation, serum glucose, calcium, magnesium, and electrolyte levels should be evaluated in terms of simple and easily corrected metabolic disorders.

In order to differentiate the presence of infection, a blood count and acute phase reactants are examined, and a lumbar puncture is performed to evaluate the cerebrospinal fluid (CSF) in patients with manifest or suspected central nervous system symptoms. A first step to determine metabolic diseases includes analysis of blood gas, lactate, serum amino acids, urine organic acids, and a tandem acylcarnitine profile. Magnetic resonance imaging (MRI) is accepted as the gold standard imaging modality.<sup>[12]</sup> However, Transfontanelle ultrasonography (US) should be performed in emergency cases where MRI is not immediately available. Infants should be monitored with continuous video EEG if possible.

There is no accepted standard diagnostic method for convulsion in the neonatal period. Neonatal convulsions are currently classified as clinical, electrographic, or electroclinical. The absence of an electrographic response to convulsions or the presence of electrographic convulsions in infants without clinical findings are frequently encountered conditions in the neonatal period. Clinical seizures may not be reflected on an EEG due to electrical activity in deep brain regions that does not reach superficial EEG electrodes.<sup>[2]</sup> An electrographic seizure is defined as the presence of epileptic discharges observed on EEG that may or may not be accompanied by clinical signs and for which the precise causes and outcomes cannot be immediately identified. Both clinical and electrographic seizures are called electroclinical seizures.

Convulsions can be diagnosed clinically; however, since electrographic activity may not be observed, and because a clinical seizure may not be seen in infants who receive sedation, the preferred method of diagnosis is continuous video EEG.<sup>[13]</sup> In a study of the diagnosis of convulsions, 91 physicians and 46 other health professionals correctly identified an average of 10 of 20 events in videos featuring 11 epileptic and 9 nonepileptic events.<sup>[14]</sup>

An evaluation of the role of EEG in the diagnosis of neonatal convulsions indicated that only 48 (27%) of 177 clinically suspected seizure episodes had a corresponding documented electrographic seizure. Clinical manifestations were observed in only 34% of a total of 526 electrographic convulsions.<sup>[15]</sup>

An amplitude EEG (aEEG) device was first used by Maynard et al.<sup>[16]</sup> in the 1960s to monitor the brain function of patients with status epilepticus. In the 1980s, it was used in the evaluation of brain function in newborns with HIE. While aEEG can be a useful diagnostic tool, disadvantages include the possibility of a false positive as the result of a spontaneous movement of the infant and the finding that only 30% of the seizures detected by conventional EEG were detected by aEEG.<sup>[17]</sup> This limits the use of aEEG in the follow-up of convulsions. Nonetheless, the use of aEEG devices is increasing for infants hospitalized in neonatal intensive care units who have manifest or suspect convulsions due to the ease of use and continuous monitoring capacity of the device.

## Treatment

Convulsion in an infant is a neuropathological condition that requires urgent diagnosis and treatment. The aim of the treatment should not only be to stop acute symptomatic seizures, but also to reduce the potential for brain damage and to minimize any possible negative effects of epilepsy or other neurological adverse effects. Many authors agree on the treatment of both electroclinical seizures and electrographic seizures. In a study that evaluated moderate and severe cases of HIE with as much as 96 hours of video EEG monitoring and assessed the neurodevelopmental status of 18- to 24-month-old infants using the Bayley Scales of Infant Development (BSID III), the authors reported that neonates treated with anticonvulsant drugs had fewer seizure events and that the scores of infants with intense seizure activity were lower than those of patients with electrographic seizures.<sup>[18]</sup>

In a case of convulsion, the possible cause should be determined once airway patency has been assured. Treatment of patients with a simple metabolic disorder is targeted to etiology.

**Hypoglycemia** When hypoglycemia is detected, 2 to 4 mL/kg 10% dextrose should be administered intravenously, followed by 6 to 8 mg/kg/minute dextrose perfusion and blood glucose monitoring.

**Hypocalcemia** Calcium gluconate (10%) should be administered by intravenous infusion at a dose of 2 mL/kg for not less than 5 to 10 minutes.

**Hypomagnesemia** Magnesium sulfate (50%) should be

administered via an intravenous or intramuscular route at a dose of 0.1 to 0.2 mL/kg.

### Anticonvulsant Drugs

**Phenobarbital** is still the first choice of initial anticonvulsant drug treatment for infants. Second options include phenytoin, levetiracetam, benzodiazepines, and lidocaine. Phenobarbital is a long-acting barbiturate derivative and is considered the principal drug for the treatment of neonatal convulsions. It acts by reducing the sensitivity of GABA  $\alpha$  receptors. The loading dose is 15 to 20 mg/kg and can be maintained with 5 mg/kg/day at 12 to 24-hour intervals. If a seizure continues for 15 fifteen minutes, an additional dose of 5 mg/kg may be given, up to a maximum of 40 mg/kg/day at 10 to 15 minute intervals. Intravenous and oral forms of phenobarbital have been used for many years, and it also has the advantage of a long half-life.<sup>[19]</sup>

Undesirable side effects can include irritability, sedation, hypotension, respiratory depression, and hepatotoxicity. Painter et al.<sup>[19]</sup> reported that seizures were controlled in 43% of neonates who received phenobarbital. In another study of primarily HIE patients, the reported effectiveness was 70%.<sup>[20]</sup> The drug has been reported to have a neuroprotective effect in HIE, but it can also cause neuronal apoptosis at doses above 40 mg/kg.<sup>[21, 22]</sup> As a result of a regression of cognitive function observed following high doses of phenobarbital, other anticonvulsant drugs have also emerged.

**Phenytoin** is an anticonvulsant drug recommended as a second line treatment that acts on voltage-dependent sodium channels. The loading dose is 15 to 20 mg/kg, and after 12 hours, maintenance therapy is initiated at a dose of 4 to 8 mg/kg/day. Although seizures were controlled in 45% of neonates in 1 study, knowledge of the pharmacokinetics remain incomplete.<sup>[19]</sup> The half-life of phenytoin can vary between 6 and 200 hours in infants within the first postnatal week of life. Another drawback is poor oral absorption.

The side effects of the prodrug fosphenytoin may be fewer, however, the pharmacokinetics are similar to those of phenytoin and the use of fosphenytoin has not been widely adopted. Animal studies have reported that phenytoin increased neuronal apoptosis at a dose of >20 mg/kg.<sup>[22]</sup> Hypotension, bradycardia, and sedation are known to be the most common side effects associated with phenytoin use during the neonatal period.

**Levetiracetam** is an anticonvulsant drug which has been used more frequently in newborns in recent years because it decreases presynaptic neurotransmitter release by binding to synaptic vesicle 2a.<sup>[23]</sup> According to the recommendations, the initial dose of levetiracetam is 10 mg/kg/day,

with a total dose of 30 mg/kg/day achieved with increases of 10 mg/kg/day every 3 days. The dose can be increased to 45 to 60 mg/kg/day in patients with resistant seizures. The availability of oral and intravenous forms is an advantage. Although there are some studies reporting that levetiracetam has good reliability and a good safety profile in newborns, the currently available evidence is still not sufficient to recommend its use as first-line therapy. Neuroprotective effects have been reported in animal studies.<sup>[24, 25]</sup> Maitre et al.<sup>[26]</sup> conducted a study of infants who experienced convulsions and were treated with either levetiracetam or phenobarbital. The BSID III test results of the patients who received phenobarbital demonstrated lower levels of cognitive, language, and motor development than those who were treated with levetiracetam. In the same study, the authors found that an increased cumulative exposure to phenobarbital was associated with cerebral palsy. In a metaanalysis of studies comparing the efficacy of phenobarbital and levetiracetam, while levetiracetam was found to be at least as effective as phenobarbital in the control of seizures, the data still do not yet support use as first-line therapy.<sup>[27]</sup>

**Midazolam** is a benzodiazepine-derived anticonvulsant drug that exhibits a GABAergic effect. It is generally used as first-line treatment of acute convulsions in children and adults, whereas it is used in the treatment of neonatal convulsions as third-line treatment. Side effects may include sedation, respiratory depression, and hypotension. Although clonazepam (0.5 mg/kg) and diazepam (10 mg/kg), from the same group, have been reported to induce apoptosis at certain doses, there is not enough data to suggest that midazolam is apoptotic.<sup>[22]</sup>

**Lidocaine** is a Class 1b antiarrhythmic drug that exerts its anticonvulsant effect by blocking voltage-gated sodium channels. The loading dose is given by intravenous infusion at a rate of 2 mg/kg within 10 minutes. The maintenance dose varies according to the weight of the infant.<sup>[28]</sup> Lidocaine-related retrospective studies are available, and in the largest neonatal case series, it was reported that the response to lidocaine varied according to the gestational weeks at birth, the underlying etiology, and the time of administration. In the same study, lidocaine and midazolam administered as the second option after phenobarbital were compared, and lidocaine was reported to be superior to midazolam. However, current data suggest that lidocaine can only be used in resistant seizures.

**Bumetanide** is a loop diuretic. It increases high sodium potassium chloride cotransporter 1 expression in neurons, and the combination with phenobarbital treatment has come to the fore. In one study, it was reported that

the use of bumetanide alone did not stop the seizure, but when bumetanide was added to phenobarbital treatment, the percentage of seizures controlled was increased.<sup>[29]</sup> However, in a study performed with the participation of 8 neonatal intensive care units in Europe, the study was discontinued due to clear side effects of bumetanide (hearing loss, hypotension, severe hyponatremia).<sup>[30]</sup> Therefore, the use of bumetanide in the neonatal period is not recommended.

**Topiramate** is known to alleviate the symptomatic convulsions by blocking AMPA receptors. It was determined that topiramate reduced the frequency of development of epilepsy in 44 newborns who were started on topiramate as HIE treatment. However, the lack of an intravenous form limits its use in the newborn.

### Treatment-resistant Convulsion

Despite the use of dual anticonvulsant drugs, convulsions may persist. Metabolic encephalopathies should be considered in unexplained resistant convulsions. Until the results of metabolic examinations are obtained, treatment should be arranged in terms of pyridoxine-dependent seizures and folinic acid-responsive seizures. In this case, a 100 mg/ kg/dose of pyridoxine should be administered intramuscularly, and if necessary, it can be given at 10-minute intervals. In case of continued convulsions, folinic acid treatment can be initiated at a dose of 4 mg/kg/g after a CSF sample is taken. The convulsions are expected to stop after 24 hours of treatment.

Although there have been many studies in the last 15 years on the efficacy of anticonvulsant drugs used in neonatal convulsions, the recommendations in the guidelines on convulsions published by the World Health Organization are lacking.<sup>[32]</sup> In addition, the fact that some acute symptomatic convulsions spontaneously regress within hours has been the subject of debate.

**Prognosis** In recent years, with developments in neonatal intensive care units, the mortality rate of infants hospitalized with the diagnosis of neonatal convulsions has decreased, but the possibility of neurological sequelae remains. The basic condition that determines the prognosis is the underlying etiology. Other factors affecting the prognosis are the number of gestational weeks at birth, birth weight, Apgar score, time of onset, and the type and duration of convulsions.

It is still not precisely known which convulsions lead to brain damage, what frequency and duration of convulsions requires treatment, and how the use of drugs may improve prognosis.

### Conclusion

Neonatal convulsions should be stopped quickly and the etiological cause should be determined. The treatment is primarily directed to the etiological cause. Phenobarbital is still the drug used as first-line treatment in infants who require an anticonvulsant drug. Levetiracetam and phenytoin are commonly used as second-line anticonvulsant drugs. Current guidelines for anticonvulsant drugs used in the newborn period still do not appear to be adequate. Therefore, large-scale, well-planned studies of anticonvulsant drugs that can be used in neonatal convulsions are required.

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