

## REVIEW ARTICLE

**Diagnosis and Treatment of Neonatal Seizures - A Review**

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Over the past few decades, the prognosis of neonatal seizures has experienced considerable enhancement due to the improvement in neonatal and infant care. The mortality rate of neonatal seizures has fallen from 40% to 20%, and the relationship between electroencephalogram (EEG) and prognosis has become quite clear. The underlying cause of seizures is a major determinant of the outcome of the disease. For example, patients with secondary seizures and hypoxic-ischemic encephalopathy have only 50% chance of normal development and total recovery, while newborns with secondary seizures and subarachnoid hemorrhage or better hypocalcemia have higher chances of recovery. Searches were conducted by two independent researchers in international (PubMed, Web of Science, Scopus, and Google Scholar) and national (SID and Magiran) databases for related studies from the inception of the databases to September 2017 (without time limitation) in English and Persian languages. It is possible to achieve accurate diagnosis through checking the history before birth and performing a thorough physical examination in some rare cases. Depending on the case, tests or additional actions can be done. EEG is the primary means for diagnosis and may exhibit paroxysmal activity in the difference between seizures or may produce electrographic seizures in cases where seizure is hidden or latent. One of the most important points in the treatment of neonatal seizures is the diagnosis of underlying cause (such as hypoglycemia, meningitis, drug deprivation, and trauma) because such diagnosis facilitates different approaches to control neonatal seizures. Most experts agree to control all clinical and electrographic seizures. Some others focus merely on clinical seizures. Most centers prefer the first approach. An important point before starting an anticonvulsant drug is to decide if the patient needs intravenous and luteinizing treatment with an initial bolus dose, or it can be easy to start treatment with a prescription for a long-acting medication based on the severity of seizure, duration, and frequency.

**Keywords:** Diagnosis, Neonatal seizures, Seizures, Treatment.**INTRODUCTION**

Over the past few decades, the prognosis of neonatal seizures has experienced a considerable enhancement due to the improvement in neonatal and infant care. The mortality rate of neonatal seizures has fallen from 40% to 20%, and the relationship between electroencephalogram (EEG) and prognosis has become quite clear.<sup>[1]</sup> Although it is very difficult to interpret neonate EEG, EEG has been found to be associated with diseases and preterm and term infants develop later in their lives. The abnormal EEG is a strong predictor of the adverse outcome of a certain disease. In addition, long electrocardiographic seizures (more than

10 min/h), periodic electrographic discharge of multifocal, and the release of electrographic seizures into the opposite hemisphere are accompanied by a weaker event.<sup>[2]</sup> The underlying cause of seizures is a major determinant of the outcome of the disease. For example, patients with secondary seizures and hypoxic-ischemic encephalopathy have only 50% chance of normal development and total recovery, while newborns with secondary seizures and subarachnoid hemorrhage or better hypocalcemia have higher chances of recovery.<sup>[3]</sup>

**METHODS****Search strategy**

Searches were conducted by two independent researchers in international (PubMed, Web of Science, Scopus, and Google Scholar) and national

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(SID and Magiran) databases for related studies from the inception of the databases to September 2017 (without time limitation) in English and Persian languages. To ensure literature saturation, the reference lists of included studies or relevant reviews identified through the search were scanned. The specific search strategies were created by a Health Sciences Librarian with expertise in systematic review search using the MESH terms and free terms according to the PRESS standard. After the MEDLINE strategy was finalized, it was adapted to search in other databases. Accordingly, PROSPERO was searched for ongoing or recently related completed systematic reviews. The key words used in the search strategy were “Diagnosis, treatment, neonatal seizures, and seizures” and Iran which were combined with Boolean operators including AND, OR, and NOT.

### Study selection

Results of the literature review were exported to Endnote. Before the formal screening process, a calibration exercise was undertaken to pilot and refine the screening. Formal screening process of titles and abstracts was conducted by two researchers according to the eligibility criteria, and consensus method was used for solving controversies among the two researchers. The full text was obtained for all titles that met the inclusion criteria. Additional information was retrieved from the study authors to resolve queries regarding the eligibility criteria. The reasons for the exclusion criteria were recorded. Neither of the review authors was blinded to the journal titles, the study authors, or institutions.

## DISCUSSION

### Diagnosis

It is possible to achieve accurate diagnosis through checking the history before birth and performing a thorough physical examination in some rare cases. Depending on the case, tests or additional actions can be done. EEG is the primary means for diagnosis and may exhibit paroxysmal activity (e.g., Sharp waves) in the difference between seizures or may produce electrographic seizures in cases where seizure is hidden or latent.<sup>[4]</sup> However, there may be some neonatal seizures not with EEG disorders

mentioned above, because of either the phenomenon of release or deep seizures and releases not measured by the scalp EEG. Similarly, electrophoretic seizures can occur without visible clinical signs. It is believed that partial development of cortical communication, which in many patients results in a lack of motility or mildness, is the main cause of such phenomenon.<sup>[5]</sup> In many neonatal intensive care units (NICUs), continuous monitoring of blinded EEGs for infants who are at risk of seizure and brain damage is a routine procedure and this, in turn, makes accurate measurements of the electrical activity of the brain and identifies seizure activity. Some centers use EEG monitoring for infants at risk even before seizures, but some other centers monitor patients who have or are at risk of seizures. In addition, attempts are made to develop methods for continuous monitoring of brain activity by self-assessment and neonatal seizure analysis, which is similar to continuous monitoring of ECG in specialized care centers.<sup>[6]</sup> In infants who receive treatment with hypothermic protocols following hypoxic-ischemic lesions, it is recommended to conduct continuous EEG monitoring during cooling and warm-up periods to detect subclinical seizures. The American Clinical Neurophysiology Association recommends conducting a neonate EEG monitoring in the NICU to allow for an EEG monitoring to provide prognosis and guidance for titration of anticonvulsant drug in infants with seizure. In infants at risk of helminthic ischemic encephalopathy, stroke, meningitis, intravesical hemorrhage, metabolic disease, and congenital anomalies of the brain and those who are paralyzed, continuous conduction of EEG provides the possibility of detecting suspected seizure clinical events and cerebral ischemia or imminent bleeding.<sup>[7]</sup> Exact neurological examination of the infant may indicate the cause of seizure. The presence of chorioretinitis suggests a congenital torch infection in the retina. Blood samples should be taken to determine blood glucose, calcium, magnesium, electrolytes, and blood urea nitrogen. If hypoglycemia is suspected, serum glucose should be measured so that treatment can be initiated immediately. Hypoglycemia can be detected alone or with hypomagnesemia. Low serum levels of calcium often accompany birth trauma or CNS damage during perinatal period. Other causes of hypoglycemia include diabetes mellitus, preterm birth, diarrhea syndrome, and high phosphate

nutrition.<sup>[8]</sup> Lumbar puncture (LP) is necessary in all newborns with seizure unless the cause of seizure is clearly associated with a metabolic disorder such as hypoglycemia or hypocalcemia. The second group of infants are natural, and alert in the interval between seizures usually respond quickly to appropriate treatment. Cerebrospinal fluid (CSF) findings may indicate bacterial meningitis or aseptic encephalitis. Rapid diagnosis and appropriate treatment improve the outcome. Blood CSF indicates LP traumatism or a subarachnoid or intravenous hemorrhage. An immediate sample centrifuge can help distinguish between these two conditions.<sup>[9]</sup> Many congenital metabolic disorders cause generalized seizures during infancy. If the blood gas indicates anion and metabolic acidosis with hyperammonemia, organic uric acid should be checked immediately for the probable presence of methylmalonic acid or propionic acid.<sup>[10]</sup> When metabolic acidosis is accompanied by generalized clonic seizures, phlebotomy, fundal, and muscle rigidity during the 1<sup>st</sup> week of life, the possibility of Maple Syrup Urine Disease must be considered. In this disease, the result of a rapid screening test using 2-4 dinitrophenylhydrazine that checks the ketone derivatives in the urine turns out to be positive.<sup>[11]</sup> Accidental injection of local anesthetic agents into the embryo can cause severe clonic seizures. Often, these babies are mistakenly thought to have had a traumatic birth because they are loose, abnormal brain reflexes, and signs of respiratory depression at the time of birth that occasionally require ventilation.

Benign familial neonatal seizures, as predominant autosomal disorders, begin on days 2–3 and frequency of seizures is 10–20 times a day. Patients are normal between seizures. Seizures stop at 1–6 months.<sup>[12]</sup> Seizures emerging on the 5<sup>th</sup> day of life (days 4–6) occur in naturally born infants; such seizures are multifocal and often last for <24 h. Diagnosis involves the exclusion of other causes of seizure and sequencing of the above genes. Such seizures have a good prognosis. Dependence on pyridoxine is a rare disorder that should be considered in a patient that has undergone generalized clonic seizures at a short distance after birth. These seizures are, especially, resistant to common anticonvulsants such as phenobarbital or phenytoin.<sup>[13]</sup>

Seizures caused by drug deprivation may be inadequate, but due to the delayed release of the drug, the baby's body can recover a few weeks

later. Drug medications include barbiturates, benzodiazepines, heroin, and methadone. The infant may be nervous, irritable, and sleepy and have experience or clear clonic seizures. Mother may deny taking medication. Urinalysis and serum analyzes can identify the responsible substance.<sup>[14]</sup>

## Treatment

One of the most important points in the treatment of neonatal seizures is the diagnosis of underlying cause (such as hypoglycemia, meningitis, drug deprivation, and trauma) because such diagnosis facilitates different approaches to control neonatal seizures. Most experts agree to control all clinical and electrographic seizures. Some others focus merely on clinical seizures. Most centers prefer the first approach. An important point before starting an anticonvulsant drug is to decide if the patient needs intravenous and luteinizing treatment with an initial bolus dose, or it can be easy to start treatment with a prescription for a long-acting medication based on the severity of seizure, duration, and frequency. Most patients need ventilation after receiving intravenous or oral administration of anticoagulants; hence, immediate intervention should be followed and necessary precaution must be taken into action.<sup>[15]</sup>

### Lorazepam

Lorazepam is the primary medication used to control acute seizures. Lorazepam is rapidly released into the brain and acts on its anticonvulsant effect in <5 min. It is not a lipophilic medication, and the speed of cleansing it from the brain is not very high. The effect can last for 6–24 h. It usually does not cause hypotension or respiratory depression.<sup>[16]</sup>

### Diazepam

Diazepam can be used as an alternative drug. Diazepam is extremely fond of fat; therefore, it is rapidly released into the brain, with a slight possibility of recurrence of seizures. Like other intravenous benzodiazepines, there is a risk of apnea and hypotension, especially if the patient is receiving barbiturate. However, due to the limitations of blood pressure and respiration and since the venous compound contains benzoic acid, it is currently not recommended as a first-line choice.<sup>[17]</sup>

**Midazolam**

Midazolam can be used as an initial drug in the form of bolus or as a second- or third-line drug in the form of continuous infusion for those who do not respond to phenobarbital and/or phenytoin.

**Phenobarbital**

Many people consider phenobarbital as the first long-acting choice in nasal calcination. Depending on clinical conditions, benzodiazepines may be used as the first-line therapy. In infants with acidosis or a severe condition that may affect serum chronitos levels, the free levels of the medication should be controlled carefully.<sup>[18]</sup>

**Phenytoin and phenytoin**

If the total loading dose was 40 mg/kg and, of course, not phenobarbital, then a loading dose of 15–20 mg per kilogram of intravenous phenytoin could be given. To prevent heart problems, the infusion rate should not be >0.5–1 mg/kg/min and it should be avoided in patients with severe heart disease.<sup>[19]</sup>

**Period of treatment**

The duration of treatment in infants with neonatal seizures depends on the risk of developing epilepsy in the future. The risk varies from 10% to 30%, depending on the patient's neurological examination, seizure etiology, and EEG profile at the time of hospital discharge. In general, if the EEG is free of paroxysmal waves at the time of discharge, the dose of the medication will decrease thereafter. If the EEG remains paroxysmal, the decision to discontinue treatment is delayed several months after discharge.<sup>[20]</sup>

**CONCLUSION**

Neonatal seizures may take many forms, with tonic-clonic movement being the least common type. Treatable causes of seizures should be evaluated before standard anticonvulsants are used. Though the mortality rate is high, survivors have a significant chance of being normal.

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