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Etiology, Onset and Treatment Strategy of Neonatal Seizures, Systemic Review

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Abstract: **Newborn infants with seizures are at risk for neonatal death and survivors at risk for neurologic impairment, developmental delay, and later epilepsy. Despite increasingly sophisticated neonatal intensive care, clinicians managing seizures remain challenged by difficult prognostic and therapeutic questions. Our objective was to determine the etiology of neonatal seizure and the proper treatment in which could be most effective for treating neonatal seizures, in order to guide development of an evidence-based treatment algorithm. We searched MEDLINE via PubMed from inception to Octorber 2016. A librarian trained in literature search strategies assisted us in the design of our search terms, which were subsequently reviewed by a second librarian. The search was limited to humans and English language articles and included the specific search terms: National Library of Medicine Medical Subject Heading [MeSH] term "Seizures/therapy" AND ("Infant, Newborn"[Mesh] OR neonat*) AND (Humans [Mesh] AND English [lang]). Phenobarbital is the preferred first drug of choice for acute treatment of neonatal seizures, both among neonatologists and paediatric neurologists. When this treatment fails, neonatologists seem to initially favour higher doses of phenobarbital while paediatric neurologists generally prefer to use other anti-epileptic medications and also more frequently off-label drugs such as levetiracetam and topiramate.**

Keywords: **Newborn infants, Etiology, Onset and treatment strategy.**

1. INTRODUCTION

Neonatal seizures occur in 1.8 per 1000 live births in the United States [(1)], with a lot of seizure activity happening in the very first couple of days of life [(2)]. Due to cerebral pathology, such as intraventricular hemorrhage and neuro developmental immaturity, early neonates of less than 30 weeks pregnancy have a greater occurrence of seizures than neonates older than 30 weeks [(2)].

Newborn infants with seizures are at risk for neonatal death and survivors at risk for neurologic impairment, developmental delay, and later epilepsy [(3,4)]. Despite increasingly sophisticated neonatal intensive care, clinicians managing seizures remain challenged by difficult prognostic and therapeutic questions [(5,6)]. In addition, speculative information has actually raised issues about the prospective negative impacts of existing treatments with barbiturates and benzodiazepines on brain advancement. Enhanced understanding of the special age-specific systems ought to yield brand-new healing targets with scientific capacity. To date, no unique substances have actually been established particularly or FDA authorized for treatment of neonatal seizures [(7)].

Developmental age-specific systems affect the generation and phenotype of seizures, the effect of seizures on brain structure and function, and the effectiveness of anticonvulsant treatment. Elements governing neuronal excitability conspire to produce a fairly hyper excitable state in the neonatal duration, as evidenced by the incredibly low limit to seizures in basic which this is the duration of greatest occurrence of seizures throughout the life expectancy [(8,9)], which likewise, in the rodent, seizure vulnerability peaks in the 2nd postnatal week in lots of designs [(6,10,11)]. In addition the insufficient advancement of neurotransmitter systems leads to an absence of "target" receptors for traditional. The factor for the increased susceptibility of the immature brain to seizure activity is the developmental stage of opposing neuroexcitatory and neuroinhibitory activity, as GABAergic synapses are functionally more active than NMDAAMPA ones and provide a net excitatory drive in the developing brain. In early life, GABA receptors have a mainly excitatory effect. This changes with progressive development when the sensitivity of the brain to seizures reduces [(12,13)].

Glutamate is the major excitatory neurotransmitter in the CNS, while γ-amino-butyric acid (GABA) is the major inhibitory neurotransmitter. There is considerable and growing evidence from animal models and human tissue studies that neurotransmitter receptors are highly developmentally regulated [6,10,14] (**Figure1**). Studies of cell morphology, myelination, metabolic process and more just recently neurotransmitter receptor expression recommend that the very first 1- 2 weeks of life in the rodent is an approximately comparable phase to the human neonatal brain. A relative over expression of specific glutamate receptor subtypes in both human and rodent establishing cortex accompanies ages of increased seizure vulnerability (**Figure1**) [10,15,16]. Glutamate receptors consist of both ligand-gated ion channels, permeable to salt, potassium, and in many cases calcium, and metabotropic subtypes [16].

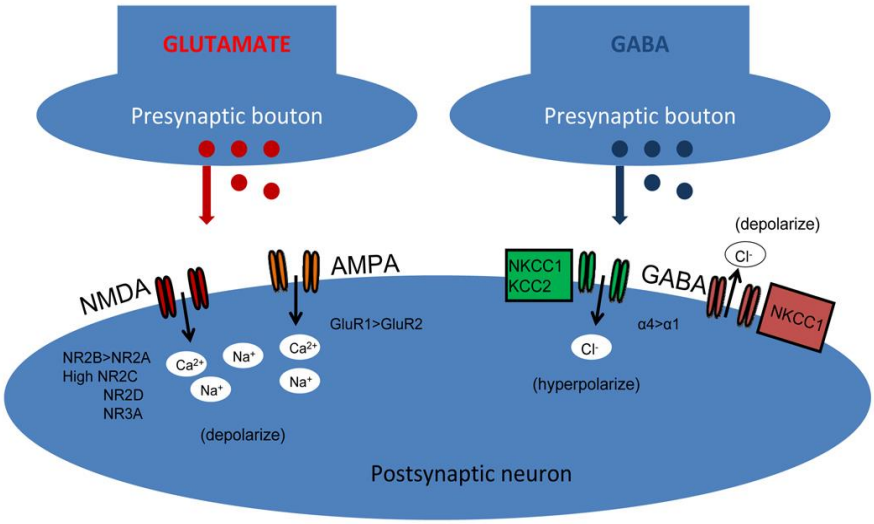

Figure1: Dynamics of synaptic transmission at cortical synapses in the neonatal period

Depicted are an excitatory glutamatergic synapse (left panel) and a GABAergic inhibitory synapse (right panel). Presynaptic release of glutamate results in depolarization (excitation) of the postsynaptic neuron (left panel) by activation of NMDA and AMPA receptors. In contrast, release of GABA (right panel) results in hyperpolarization (inhibition) when the post synaptic neuron expresses sufficient quantities of the Cl^- transporter KCC2, but depolarization (excitation) when intracellular Cl^- accumulates due to unopposed action of the Cl^- importer NKCC1. The immature glutamatergic receptors (left panel) are comprised of higher levels of NR2B, NR2C, NR2D, and NR3A subunits of the NMDA receptor, enhancing influx of Ca^{2+} and Na^+ compared to mature synapses [8].

We conducted a systematic review to evaluate the published evidence regarding the etiology and treatment strategies for neonatal seizures. Our objective was to determine the etiology of neonatal seizure and the proper treatment in which could be most effective for treating neonatal seizures, in order to guide development of an evidence-based treatment algorithm.

2. METHODOLOGY

Study design:

The systematic review was conducted following the general principles published by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [17].

Search strategy:

We searched MEDLINE via PubMed from inception to Octorber 2016. A librarian trained in literature search strategies assisted us in the design of our search terms, which were subsequently reviewed by a second librarian. The search was limited to humans and English language articles and included the specific search terms: National Library of Medicine Medical Subject Heading [MeSH] term "Seizures/therapy" AND ("Infant, Newborn"[Mesh] OR neonat*) AND (Humans [Mesh] AND English[lang]). Upon reviewing references from articles in the original search, we included additional relevant manuscripts that met our inclusion criteria.

Inclusion and Exclusion Criteria:

We only included articles that focused on diagnosis and etiology of neonates seizure and its treatment, defined as infants less than or equal to 30 days postnatal age. Since neonatal seizures are often misdiagnosed by clinical impression

alone. Case reports, review articles with no primary data, and non-peer reviewed studies including meeting abstracts were excluded, as were articles that did not include seizure cessation as an outcome.

Data Extraction:

All authors independently reviewed each title and abstract to determine eligibility. Whenever the abstract did not reveal sufficient information about the study design, the full article was retrieved for review. All authors reviewed all papers that were deemed potentially eligible following abstract review using a structured checklist to evaluate study design, methods, results, potential for study bias, and adverse events.

3. RESULTS AND DISCUSSION

Etiology of neonatal seizures:

Two of our included studies [2,3] found that the most typical reason for symptomatic neonatal seizures is hypoxic/ischemic encephalopathy (HIE), which impacts around 1- 2/1000 live births [2,3]. One research study revealed that about two-thirds of cases of neonatal seizures are due to HIE [4]. These seizures can take place in the setting of birth asphyxia, breathing distress, or as a problem of early life extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass for restorative heart surgery [5]. When it comes to HIE, these seizures normally take place within the very first 1- 2 days of birth and typically remit after a couple of days, however bring with them a threat of long-lasting epilepsy and neurological/cognitive deficits [18,19]. HIE is connected with a high occurrence of seizures, supposedly in 40–60% of cases [20,21].

We also identified one very important study [5] involving Eighty-nine infants with clinical neonatal seizures underwent neurologic examination, electroencephalography (EEG), neuroimaging, and extensive diagnostic tests in the newborn period. After discharge, all infants underwent regular neurologic evaluations and, at 12 to 18 months, formal neurodevelopmental testing. Then they showed that the distribution of etiologies for the neonatal seizures in 89 infants is presented in **Table 1**. The most common etiologies for neonatal seizures were global cerebral HI, cerebral vaso-occlusive lesions, and intracranial hemorrhage. Of note, none of our infants had toxin exposure; drug withdrawal; or familial, genetic, or syndromic causes for their seizures. Among the 23 infants with intrapartum asphyxia, 10 had moderate and 13 had severe encephalopathy. By definition, no infant had mild encephalopathy because seizures placed infants in at least the moderate level of encephalopathy [5].

Table1: Etiologic Distribution of Clinical Neonatal Seizures (n89) [5]

Global cerebral HI	N (%) 36 (40)
Intrapartum cerebral HI	23
Antepartum cerebral HI	10
Postnatal cerebral HI	3
Focal cerebral HI	16 (18)
Arterial infarct	13
Venous infarct	3
Intracranial hemorrhage	15
Extraparenchymal hemorrhage	11
Intraparenchymal hemorrhage	2
Cerebral dysgenesis	5
Transient metabolic disturbance	3 (4)
Hypoglycemia	2
Hypocalcemia hypomagnesemia	1
Infection	3 (3)
Inborn error of metabolism	1(1)
Etiology unknown	11 (12)

In other three studies acute transient metabolic disturbances and central nervous system infections were less commonly implicated as the cause of neonatal seizures than in earlier studies [22,23,24]. In fact, seizures caused by transient metabolic disturbances (eg, hypoglycemia and electrolyte disturbances) show a 10-fold decrease compared with other reports over the past 30 years. It is likely that improved neonatal intensive care is at least partly responsible for this trend, just as improved maternal and neonatal antimicrobial strategies are likely a reason for the marked decrease in seizures resulting from central nervous system infections [23,24].

Five studies [25,26,27,28,29] found that the cerebral hemorrhage has been the leading cause for neonatal seizures in most previous studies, although the incidence has varied, likely as a result of the inconsistent diagnostic criteria used. Although global cerebral hemorrhage remains the most common etiology for seizures in our study, there are distinct differences from previous reports.

Treatment strategy of Neonatal Seizures:

Phenobarbital is the preferred first drug of choice for acute treatment of neonatal seizures, both among neonatologists and paediatric neurologists. When this treatment fails, neonatologists seem to initially favour higher doses of phenobarbital while paediatric neurologists generally prefer to use other anti-epileptic medications and also more frequently off-label drugs such as levetiracetam and topiramate. The second choice anti-epileptic drug for neonatal seizures is phenytoin [30,31,32,33,34]. Reasons for choosing these antiepileptics included fewer adverse effects and ease of use [34].

Benzodiazepines and lidocaine are other drugs commonly used for anti-epileptic treatment. Although these drugs were only compared in a small randomised controlled trial [30], they are commonly used and several observational studies have investigated their acute effects and pharmacokinetics [36]. Two studies investigated neonatologists' and paediatric neurologists' preferred treatments of seizures in preterm infants, which were very similar to that of term infants [37,38]. Most neonatal seizures are entirely subclinical. Although some experimental data indicate that subclinical seizures may also be detrimental for brain function, clinical data supporting these findings are scarce. During the last decade, an ongoing debate has been whether subclinical seizures should be treated or not, not least in the light of possible adverse effects of anti-epileptic drugs on brain development [39]. Bassan et al. addressed this dilemma; when asking whether neonatal electrographic seizures could be harmful for the brain, 38% of paediatric neurologists and 34% of neonatologists said yes, while 47% and 43%, respectively, replied that they did not know [40]. Forty per cent of the paediatric neurologists and 38% of the neonatologists would treat electrographic seizures, while 30% and 35% would not and the remaining said they did not know. It is our impression that these figures reflect much of the overall debate regarding treatment of subclinical neonatal seizures [41].

one study [42] stated dosage regimens for phenobarbital and benzodiazepines are less complex than those for phenytoin in the neonatal population, they may be less effective due to the receptor and ion gradient variations in the neonate described previously (**Figure 2**). A decreased response with benzodiazepines and phenobarbital may be expected as the inhibitory GABA receptors targeted are underexpressed in the neonatal brain. Immature GABA receptors overexpress the α_4 subunit compared to the α_1, which has been shown to decrease responsiveness to benzodiazepine therapy. Consideration has to be given to the reversed Cl^- gradient [35,42]. Activation of the GABA receptor in a mature brain allows for the opening of a Cl^--selective pore, the influx of Cl^- along its gradient, and the hyperpolarization of the cell. However, in the immature neonatal brain, GABA activation by an agonist leads to an efflux of Cl^- due to the high intracellular concentrations, which may cause depolarization of the membrane resulting in neuronal firing [42].

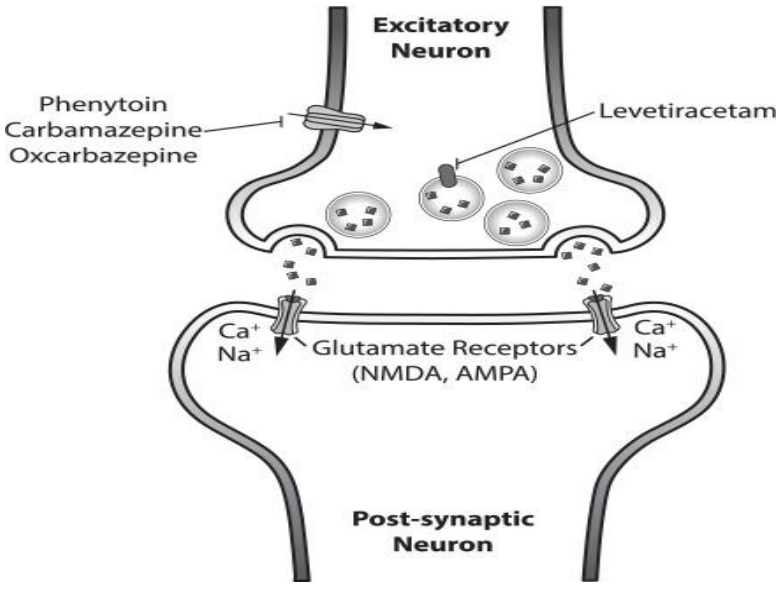

Figure2: Pre and post excitatory neuron with neurotransmitter, glutamate. Mechanism of action of common antiepileptics depicted.

4. CONCLUSION

The most common cause of symptomatic neonatal seizures is hypoxic/ischemic encephalopathy (HIE). These seizures can occur in the setting of birth asphyxia, respiratory distress, or as a complication of early life extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass for corrective cardiac surgery. Other cerebrovascular disorders including arterial and venous stroke, intracerebral hemorrhage and subarachnoid hemorrhage also frequently present clinically with seizures. Aside from HIE and cerebrovascular causes, the next most common causes of neonatal seizures are infectious etiologies and malformations of cortical development. Common bacterial infections causes include Group B streptococcus and Escherichia coli. Nonbacterial causes include intrauterine toxoplasmosis or cytomegalovirus infection, or neonatal encephalitis due to toxoplasmosis, herpes simplex, coxsackie, or cytomegalovirus. Malformations of cortical development that frequently present with early life seizures include lissencephaly, polymicrogyria, focal cortical dysplasia, and tuberous sclerosis Metabolic disturbances responsible for neonatal seizures include hypoglycemia, hypocalcemia, hypomagnesemia, and abnormalities of other electrolytes and amino acids. Phenobarbital is the preferred first drug of choice for acute treatment of neonatal seizures, both among neonatologists and paediatric neurologists. When this treatment fails, neonatologists seem to initially favour higher doses of phenobarbital while paediatric neurologists generally prefer to use other anti-epileptic medications and also more frequently off-label drugs such as levetiracetam and topiramate.

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