Prematurity and Neonatal Epileptic Syndromes: A Narrative Review on Cognitive Functioning Implications

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Abstract

Prematurity is a medical condition that is frequently associated with various prenatal factors and carries an increased risk of perinatal complications, such as epileptic seizures. Without medical management, the frequency and severity of seizures may compromise neurological development, potentially affecting the neonate's overall health and long-term cognitive functioning. This narrative review aims to synthesize both past and contemporary literature to elucidate the influence of epilepsy on the cognitive development of preterm neonates. A literature search was performed for the keywords "Prematurity" OR "Preterm" AND "Neonates" OR "Infants" AND "Epileptic Syndromes" OR "Epilepsy" AND "Cognitive Functioning" OR "Neurodevelopmental Outcomes" in PubMed, ScienceDirect, and CINAHL databases. In addition, a snowball search method was carried out by tracking down related works by using the bibliography or reference list at the end of an article. Overall, this narrative review underlines the mechanisms underlying the increased vulnerability of the immature brain to seizures and their long-term effects on developmental trajectories. Furthermore, the importance of early diagnosis, advancements in neuroimaging, and therapeutic approaches to mitigate long-term impacts are also highlighted. Gaps in current research and clinical practice are systematically examined to facilitate the formulation of targeted strategies intended to enhance the quality of life and cognitive outcomes in preterm neonates with epilepsy.

Keywords: prematurity, epileptic syndromes, epilepsy, cognitive functioning

JEL Classification Codes: I10, J13

Introduction

Prematurity is a significant medical condition defined as the birth of a neonate before the 37th week of gestation (Ohuma et al.,2023). This early delivery is frequently associated with various prenatal factors and carries an increased risk of perinatal complications, which, in the absence of timely medical intervention, can adversely affect survival. Among the most prevalent complications observed in preterm neonates is epilepsy—a chronic neurological disorder characterized by abnormal neuronal activity resulting in recurrent seizures (Perin et al.,2022).

The prevalence of epilepsy in preterm neonates ranges from 0.75% to 2.8%, with its occurrence influenced by factors such as the degree of prematurity, birth weight, and the presence of perinatal complications

(Hirvonen et al., 2017). Risk factors include hypoxic-ischemic encephalopathy, intraventricular hemorrhage, infections, and neuroinflammation (Pisani et al., 2021). Without adequate medical management, the frequency and severity of seizures may compromise neurological development, potentially affecting the neonate's overall health and long-term cognitive outcomes (Pisani et al.,2021; Schüssler et al., 2022).

The progressive nature of epilepsy in this population is particularly concerning, as it is associated with impaired cognitive functions, including deficits in memory, learning, and attention (Akter et al.,2024). These cognitive challenges underscore the critical need for early identification and intervention to mitigate the long-term impact of epileptic seizures. This narrative review aims to synthesize both past and contemporary literature to elucidate the impact of epilepsy on the cognitive development of preterm neonates. By mapping the current understanding of this relationship, the review seeks to inform strategies for improving outcomes in this vulnerable population.

Methodology

Narrative review

A literature search was performed for the keywords "Prematurity" OR "Preterm" AND "Neonates" OR "Infants" AND "Epileptic Syndromes" OR "Epilepsy" AND "Cognitive Functioning" OR "Neurodevelopmental Outcomes" in PubMed, ScienceDirect, and CINAHL databases. The inclusion criteria of the articles retrieved were the following: 1) studies from 2014 to present 2) articles written in English 3) studies about preterm neonates as a target group who exhibited epileptic syndromes 4) studies about preterm neonates' neurodevelopmental outcomes focusing on cognitive functioning. In addition, a snowball search method was carried out by tracking down related works by using the bibliography or reference list at the end of an article. In this narrative review, 137 articles were identified via database and citation searches. After reviewing the titles and abstracts, a total of 70 studies were included. The reviewed articles included reports about definition, categorization and risk factors of preterm birth, epileptic syndromes and seizures, diagnosis and assessment methods, as well as the impact of preterm neonates' epileptic syndromes on their later cognitive development.

Preterm Birth and Neurodevelopmental Complications

Definition and Categorization of Preterm Birth

Preterm birth, characterized by the delivery of a neonate prior to 37 weeks of gestation, has shown an increasing prevalence over the past decade (UNICEF, 2023). According to the World Health Organization (WHO), approximately 13.4 million neonates are born preterm each year (WHO, 2023). Prematurity is the leading cause of mortality in children under five years old, contributing to more than 20% of deaths in this age group (Pan American Health Organization, 2023).

The survival of preterm neonates is closely linked to the severity of prematurity, with risk inversely proportional to gestational age at birth.

Extremely preterm infants, born before 28 weeks of gestation, face the highest risk, followed by very preterm (<32 weeks), moderate preterm (<34 weeks), and late preterm infants (<37 weeks) (Abdallah et al., 2021). These categories provide a framework for understanding the degree of prematurity and its associated health implications.

Improved perinatal care in neonatal intensive care units (NICUs) is associated with a reduction in mortality in extremely preterm infants, even at 76% of preterm births (Norman et al, 2019). The development of technological equipment related to medical practice, along with the training and education of nursing staff in neonatal clinics are beneficial in improving the health status of the preterm neonate (Pearlman & Inder, 2024). However, the reduction in mortality in preterm neonates does not translate into a corresponding reduction in the restrictions they develop during childhood and adulthood (Linsell et al., 2018).

Risk factors and Neurodevelopmental Implications in Preterm Neonates

Preterm birth interrupts the normal progression of brain development, leaving the central nervous system (CNS) neurologically immature and vulnerable to a range of adverse conditions. Several factors contribute to this vulnerability, including:

- **Incomplete development of brain structures**, such as cortical gyri, sulci, and white matter (Wallois et al., 2020).
- **Increased susceptibility to traumatic brain injury** due to fragile blood vessels (DeMaster et al., 2019).
- **Impaired regulation of oxygen supply and cerebral blood flow.**
- **Delayed myelination** stemming from underdeveloped oligodendrocytes.
- **Reduced brain volume**, particularly in structures like the hippocampus, cerebellum, and gray matter (Haffner & Sankovic, 2022).
- **Immature antioxidant defense systems** in the brain (Jain et al., 2021).

These factors commonly result in neurodevelopmental complications that hinder normal brain function in preterm neonates (Haffner & Sankovic, 2022). Specific conditions include:

Intraventricular Hemorrhage (IVH): IVH arises from the fragility of blood vessels in the periventricular germinal matrix, often extending into the brain parenchyma, leading to hydrocephalus or white matter damage. IVH increases the risk of cerebral palsy and cognitive deficits, impacting the neonate's overall intellectual capacity (Novak et al., 2018).

Periventricular Leukomalacia (PVL): PVL is characterized by ischemia in the periventricular white matter, typically due to oxygen deprivation or inflammation. This condition negatively affects oligodendrocyte maturation and myelin production, resulting in motor impairments such as spastic diplegia and cognitive deficits in executive function and attention (Pearlman & Inder, 2024).

Hypoxic-Ischemic Encephalopathy (HIE): Hypoxic and ischemic events, whether during or after birth, disrupt cerebral oxygen supply, making the brain vulnerable to neuroinflammation and neuronal death. HIE is associated with

seizures, epilepsy, and developmental delays in affected neonates (Inder & Volpe, 2024).

Restricted Brain Growth: The rapid brain development that occurs during the third trimester is often halted due to premature birth. This interruption leads to smaller brain volumes, delayed cortical folding, and underdeveloped subcortical structures. Neurodevelopmental disorders are correlated with reduced cognitive potential, memory impairments, and learning difficulties(Novak et al., 2018).

Neuroinflammation: Preterm neonates are prone to perinatal infections such as chorioamnionitis and systemic inflammation. Hyperactivation of microglia and cytokines (e.g., IL-6, IL-1β) can become neurotoxic when sustained, leading to oxidative stress, neuronal damage, and long-term cognitive and behavioral difficulties (Jain et al., 2021).

Neonatal Seizures and Epilepsy

Preterm neonates often exhibit underdeveloped inhibitory neuronal networks responsible for regulating neural activity. Immature inhibitory mechanisms allow excitatory neurons to fire uncontrollably, leading to seizures. Recurrent seizures, if untreated, can disrupt long-term brain development, contributing to chronic epilepsy and cognitive or motor deficits.

Definition and Types of Epileptic Syndromes

Epilepsy is a chronic neurological disorder characterized by a predisposition to generate unprovoked seizures due to abnormal brain activity. It is defined by the International League Against Epilepsy (ILAE) as a condition of the brain with at least one of the following: (1) two or more unprovoked (or reflex) seizures occurring more than 24 hours apart; (2) one unprovoked (or reflex) seizure and a high probability of further seizures over the next 10 years; or (3) the diagnosis of an epilepsy syndrome (Zuberi et al., 2022). Globally, epilepsy affects approximately 50 million individuals, making it one of the most prevalent neurological disorders (World Health Organization, 2022). Seizures in epilepsy are the clinical manifestation of transient, excessive, and synchronized neuronal discharges in the brain, which can result in various motor, sensory, autonomic, or cognitive challenges (Stafstrom & Carmant, 2015).

Epileptic syndromes in neonates encompass a variety of clinical presentations, often categorized by the onset of seizures, the nature of the seizures, and underlying etiological factors (Zuberi et al., 2022). Neonatal seizures are one of the most common neurological emergencies in the neonatal period, with substantial implications for long-term neurodevelopmental outcomes. Epileptic seizures in neonates can be classified into several types, including neonatal seizures, hypotonic seizures, and myoclonic seizures, each having distinct features and diagnostic considerations (Andreolli et al., 2019).

Neonatal Seizures and Their Classification

Neonatal seizures are a key clinical feature of early-onset epilepsy and can manifest as a wide range of seizure types. These include *hypotonic seizures, myoclonic seizures, and neonatal seizures* of various origins, each associated with different epileptic syndromes (Pressler et al., 2021; Ziobro & Shellhaas, 2020).

- **Atonic seizures:** These seizures are characterized by a sudden loss of muscle tone, resulting in a "floppy" appearance of the neonate (Kim et al., 2022; Pressler et al., 2021). Atonic seizures are typically seen in the context of *focal epileptic syndromes*, such as those caused by perinatal insults (e.g., hypoxic-ischemic encephalopathy), structural brain malformations, or infections (Pressler et al., 2021). In these cases, the seizures often originate from a specific brain region, and their manifestation can include a generalized loss of muscle tone, which makes them difficult to differentiate from other non-epileptic conditions such as sleep states or metabolic disturbances.
- **Myoclonic Seizures:** Myoclonic seizures involve sudden, brief muscle jerks, which can appear as if the infant is having involuntary, rapid movements (Kim et al., 2022; Pressler et al., 2021). These seizures are commonly seen in *generalized epileptic syndromes, such as Juvenile Myoclonic Epilepsy (JME) and Dravet syndrome*, although they can also appear in the neonatal period as part of severe metabolic or structural brain disorders. In neonates, myoclonic seizures may occur in conjunction with other seizure types, such as tonic-clonic seizures, and are often associated with a poor neurodevelopmental prognosis if untreated.
- **Neonatal Seizures:** These seizures typically present as focal events, reflecting the immature connectivity of the neonatal brain (Ramantani et al., 2019). Neonatal seizures are often caused by perinatal insults, including hypoxia, infections, or metabolic disturbances. Focal seizures may manifest as repetitive movements, abnormal posturing of a single limb, or subtle signs such as lip smacking or eye deviations. Focal seizures, originating from one hemisphere of the brain, may manifest as repetitive movements or abnormal posturing of a single limb.

Focal, Generalized, and Combined Epilepsies in Neonates

Epileptic syndromes in neonates can be further classified based on the nature of the seizure activity and the areas of the brain involved. These classifications help clinicians determine the appropriate diagnostic workup and treatment options for the infant (Pressler et al., 2021).

- **Focal Epilepsies:** Focal seizures are confined to one specific region of the brain, which is often associated with structural abnormalities or localized brain injury (Danzer, 2019). In the neonatal period, focal epilepsies may be caused by factors such as perinatal hypoxia-ischemia, infections, or brain malformations. The seizures are typically unilateral and can manifest as focal motor movements, abnormal posturing, or eye deviation. Focal neonatal seizures are important to identify early because they may have a better prognosis with appropriate treatment compared to generalized seizures (Ziobro & Shellhaas, 2020).
- **Generalized Epilepsies:** Generalized epilepsies involve bilateral, synchronous discharges affecting both hemispheres of the brain (Pressler et al., 2021). These syndromes often have an onset in infancy or early childhood. *West syndrome* is a key example of generalized epilepsy, marked by infantile spasms that are often followed by developmental regression and a characteristic hypsarrhythmia pattern on EEG (Pavone et al., 2020). West syndrome typically emerges in the first year of life, often in the neonatal period, and represents one of the most severe epileptic syndromes in infancy. In West syndrome, the seizures are "spasms," which are generalized and involve the body's trunk and limbs. These seizures tend to occur in clusters and are often associated with developmental delay (Barbarrosa et al., 2020). As a generalized

syndrome, West syndrome is sometimes classified as a form of combined generalized epilepsy because it can evolve into other generalized syndromes such as Lennox-Gastaut syndrome(Hirsch et al., 2022).

- **Combined Focal and Generalized Epilepsies**: Some epileptic syndromes feature both focal and generalized seizure types, representing a more complex seizure phenotype. Dravet syndrome, for example, is a severe epilepsy syndrome characterized by febrile seizures in infancy, followed by a mix of generalized and focal seizures as the child grows older (Anwar et al., 2020) Lennox-Gastaut syndrome also falls into this category, presenting with tonic seizures, developmental regression, and a combination of both focal and generalized seizure types (Strzelczyk & Schubert-Bast, 2021). In the case of West syndrome, although it starts with primarily atonic seizures in the neonatal period, it can evolve into a broader epileptic syndrome that may eventually exhibit mixed focal and generalized seizures, further complicating its classification.

Differences in Preterm Neonates Compared to Full-Term Neonates

The occurrence of epileptic seizures in preterm neonates differs substantially from that in full-term neonates (Pisani et al., 2018). Prematurity is associated with an increased risk of neonatal seizures due to the underdevelopment of the brain, particularly in areas responsible for motor control, sensory processing, and coordination. Preterm neonates are more vulnerable to perinatal insults such as intraventricular hemorrhage, hypoxic-ischemic encephalopathy, and infections, all of which can predispose to the development of seizures. Additionally, the brain's immature neurotransmitter systems, ion channels, and synaptic structures contribute to an increased likelihood of seizures in the preterm infant. Seizure onset in preterm neonates may also occur earlier than in full-term neonates, and the types of seizures observed may be more diverse, often requiring specialized interventions.

Etiology and Risk Factors

The etiology of neonatal epilepsy is multifactorial, and various perinatal, genetic, and metabolic factors contribute to the occurrence of epileptic seizures in neonates. Identifying the underlying causes is essential for accurate diagnosis, prognosis, and treatment, as management strategies often differ depending on the etiology.

Perinatal Factors

Hypoxia-Ischemia: Hypoxic-ischemic is often the result of birth asphyxia, placental insufficiency, or umbilical cord complications. The resulting brain injury can lead to structural brain damage, which predisposes neonates to seizure activity. Hypoxic-ischemic encephalopathy can lead to both acute and chronic neurologic sequelae, including cerebral palsy and cognitive impairments, particularly when seizures are not well-controlled (Kaur & Pappas, 2020).

Infections: Infections can be either prenatal (e.g., intrauterine infections like cytomegalovirus or toxoplasmosis) or postnatal (e.g., bacterial meningitis, sepsis, or viral infections). Infection-induced brain inflammation can result in a variety of neurological complications, including seizures. Furthermore, certain infections can lead to the

development of more severe epileptic syndromes, such as neonatal meningoencephalitis or encephalopathy, which are often associated with intractable seizures (Pisani et al., 2021).

Intraventricular Hemorrhage (IVH): IVH occurs when there is bleeding into the ventricles of the brain, typically due to the fragility of the blood vessels in the immature brain of preterm infants. The presence of IVH increases the likelihood of seizure activity, and the severity of the hemorrhage is often correlated with the risk of both acute and long-term neurological sequelae, including developmental delays, motor impairments, and seizures (Nickels & Noe, 2021).

Genetic and Metabolic Factors

Genetic Factors: Certain genetic mutations are associated with neonatal seizures and epileptic syndromes. These mutations often involve genes responsible for ion channel function, neurotransmitter regulation, or brain development. Genetic epilepsies, such as Benign Familial Neonatal Epilepsy (BFNE), which involves mutations in potassium channel genes (e.g. KCNQ2 or KCNQ3), can present with recurrent seizures in the neonatal period. Other genetic syndromes, such as early-onset epileptic encephalopathies (e.g. Ohtahara syndrome), are linked to mutations in genes like STXBP1 or ARX (Ziobro & Shellhaas, 2020). These genetic factors can contribute to both the onset of seizures and the development of more severe epileptic syndromes.

Metabolic Disorders: Metabolic disorders are another key etiology for neonatal seizures. Inborn errors of metabolism, such as urea cycle disorders, mitochondrial diseases, and hypoglycemia, can lead to imbalances in biochemical pathways, resulting in neurotoxic effects that provoke seizure activity. Identifying metabolic abnormalities through biochemical and genetic testing is crucial in managing these, as early intervention can prevent further neurological damage because some inborn errors of metabolism are treatable.

Diagnosis and Clinical Assessment

Accurate diagnosis and clinical assessment are critical to identifying the underlying cause of neonatal seizures and guiding appropriate management. The diagnostic process involves a combination of clinical evaluation, neurophysiological testing, and imaging studies.

Use of EEG (Electroencephalogram)

Electroencephalography (EEG) is the gold standard for diagnosing and monitoring neonatal seizures (Kim et al., 2022). EEG provides real-time information on the electrical activity of the brain, allowing for the identification of seizure patterns, localization of seizure foci, and assessment of the brain's overall electrical stability (Pressler et al., 2021). In neonates, EEG can detect interictal epileptiform discharges (abnormal brain waves between seizures) that can help establish the diagnosis of epilepsy. Moreover, it can differentiate between true seizures and non-seizure phenomena (e.g., myoclonus or benign movements) that may mimic seizure activity (Okumura, 2020). The use of continuous video-EEG

monitoring is particularly helpful in neonates who are critically ill or unresponsive to initial treatment.

Imaging Methods (MRI, Ultrasound)

Neuroimaging plays a pivotal role in diagnosing the underlying causes of neonatal seizures (Coryell et al., 2018). Magnetic resonance imaging (MRI) is the most sensitive imaging modality for detecting structural brain abnormalities, such as cortical malformations, intraventricular hemorrhage, or hypoxic-ischemic injury. MRI findings can provide insight into the severity of brain damage and help determine whether there are any reversible or treatable causes of seizures (Kim et al., 2022). For preterm neonates, cranial ultrasound is often used as an initial screening tool, given its accessibility and the ability to detect major abnormalities such as intraventricular hemorrhage. Ultrasound is especially valuable in the early neonatal period, where MRI may be more difficult to perform due to the infant's size or medical condition (Lescrauwaet et al., 2022).

Importance of Early Diagnosis

Early diagnosis of neonatal seizures is crucial for effective management and improving long-term outcomes (Ziobro & Shellhaas, 2020). Seizures in neonates can be a sign of underlying brain injury, and prolonged or untreated seizures can lead to irreversible neurological damage. Prompt identification of the seizure type and underlying etiology allows for the initiation of targeted treatments, such as antiseizure medications, and can help prevent further brain injury. Moreover, early diagnosis provides the opportunity for monitoring and addressing any potential developmental delays or cognitive impairments, offering the possibility of early interventions that can optimize the child's long-term development. Furthermore, early diagnosis enables clinicians to assess prognosis more accurately, helping parents and caregivers understand the potential trajectory of the condition. It also helps guide decisions regarding neonatal intensive care, as well as future care and surveillance needs for the child.

Impact on Cognitive Development

Relationship Between Epilepsy and Cognitive Development

The relationship between epilepsy and cognitive development is particularly significant in preterm neonates, given their heightened vulnerability due to incomplete neurodevelopment at birth. The brain of a preterm infant is in a critical stage of maturation, characterized by rapid growth, differentiation, and synaptogenesis (Volpe, 2019). Seizures during this period can have profound implications, disrupting neurodevelopmental processes and leading to long-term cognitive and behavioral impairments, with effects that vary depending on the timing, frequency, and severity of seizures (Vesoulis et al., 2021).
The impact of epilepsy on cognitive functioning varies widely but often includes deficits in specific domains:

- **Memory and Learning**: Damage to the hippocampus and associated networks can lead to episodic memory impairments and difficulty forming new memories (Novak et al., 2022). Prolonged epileptic activity disrupts working memory, a key cognitive function required for temporarily

holding and manipulating information. This impairment can hinder problem-solving abilities, reduce comprehension, and negatively impact tasks such as mental arithmetic or following multi-step instructions (Menlove & Reilly, 2015).

- **Attention and Executive Function:** Frequent seizures and abnormal cortical activity can impair attention, decision-making, and planning, particularly in tasks requiring sustained focus (Reuner et al., 2016). Epilepsy frequently disrupts attentional control and executive functions, which are mediated by the prefrontal cortex and its connections to other brain regions (Zanaboni et al., 2021). Children and adults with epilepsy may struggle with maintaining sustained attention, switching focus between tasks, and inhibitory control, particularly in the context of frequent seizures or interictal epileptiform discharges (Reuner et al., 2016). These difficulties often translate into challenges in decision-making, planning, and organization. The impact is especially pronounced in individuals with generalized epilepsies, where widespread cortical activity can impair global cognitive processes.
- **Language Development:** Seizures that involve the temporal lobe or other language-related areas can have profound effects on speech and language development (Bailey & Im-Bolter, 2021). In children, early-life seizures in these regions may delay speech acquisition and impair language comprehension, affecting vocabulary development and grammatical skills (Caplan, 2019). Damage to specific areas, such as Broca's area or Wernicke's area, may lead to expressive or receptive language deficits, respectively. These deficits can persist into adulthood if not addressed through early interventions.
- **Social Cognition and Emotional Regulation:** Epilepsy often affects social cognition, which encompasses the ability to recognize, interpret, and respond to social cues (Steiger & Jokeit, 2017). Disruptions in the frontal and limbic circuits, including the amygdala, can impair emotional regulation, making it challenging for individuals to manage frustration, anxiety, or impulsivity (van den Berg et al., 2018). Children with epilepsy frequently exhibit difficulties in forming and maintaining peer relationships, partly due to challenges in understanding social nuances or emotional expressions. These issues are compounded by the stigma associated with epilepsy, which may lead to social withdrawal or isolation.

Effects of Seizures During Critical Developmental Periods

Seizures that occur during critical periods of development, when the brain is highly sensitive to environmental and intrinsic stimuli, can interfere with the establishment of neural networks essential for cognitive functions such as memory, attention, and language. For instance, seizures in the hippocampus, a region integral to learning and memory, can lead to structural and functional abnormalities, compounding the cognitive deficits observed in preterm infants. Seizures disrupt the synchronization needed for these circuits to form correctly, leading to inefficient or incomplete networks. A central mechanism affected during these periods is synaptic plasticity, the brain’s capacity to adapt and reorganize. Seizures can drive maladaptive plasticity, where aberrant connections are reinforced while beneficial pathways are weakened or fail to form. This imbalance hinders learning and adaptation, compounding the challenges posed by disrupted neural circuitry (Lignani et al., 2020). Additionally, seizures impose significant metabolic demands on the developing brain. This increased activity can lead to hypoxia or excitotoxicity, damaging vulnerable neurons. Neuroinflammation, often a secondary effect of seizures, exacerbates this damage, further impairing the brain's ability to develop normally (Sanz et al., 2024).

Certain brain regions are particularly sensitive to the effects of early-life seizures. The hippocampus, a structure critical for memory and learning, is especially prone to damage, leading to persistent deficits in episodic memory (Niedecker et al., 2021). Similarly, disruption in the prefrontal cortex during this stage can impair executive functions such as decision-making, impulse control, and attention (Ruggiero et al., 2024). The thalamus, a vital relay center for sensory processing and cortical communication, is another area where epileptic activity can have profound effects, impacting sensory integration and higher-order brain functions.

By interfering with these foundational processes, seizures during critical developmental windows pose significant challenges to achieving optimal neurocognitive outcomes (Anwar et al., 2020). Understanding these effects underscores the urgency of early diagnosis and intervention to mitigate long-term impacts.

Neuroplasticity in Preterm Neonates

Neuroplasticity refers to the brain's ability to reorganize and adapt in response to injury or environmental changes (Mateos-Aparicio & Rodríguez-Moreno, 2019). While the immature brain demonstrates a remarkable capacity for compensation, excessive or recurrent seizures can overwhelm these adaptive mechanisms. Disruptions in neural connectivity and alterations in synaptic architecture, often induced by epileptic activity, can impair cognitive development and hinder recovery from perinatal brain injuries.

Early Intervention

Timely therapeutic interventions are critical in mitigating the cognitive impact of epilepsy in preterm infants, a group that is particularly vulnerable to neurodevelopmental challenges due to their underdeveloped brain structures at birth (Khurana et al., 2020). Early developmental therapies, including physical therapy, occupational therapy, and speech therapy, have been shown to enhance neuroplasticity, the brain's ability to reorganize and form new neural connections (Mercier & Dorris, 2024). This ability to adapt is crucial for the brain to recover from the negative impacts of seizures and promote the acquisition of age-appropriate developmental milestones.

Studies indicate that interventions during critical periods of development, especially in the neonatal and infant stages, can significantly improve cognitive, motor, and language outcomes. Randomized controlled trials on preterm infants demonstrate that early therapeutic interventions, including motor-based therapies, significantly improve cognitive and motor skills at later stages of development, with some benefits extending into preschool years (Stedall et al., 2022). These findings are supported by a Cochrane review, which concluded that early developmental programs likely improve both cognitive and motor outcomes during infancy, although the long-term effects vary (Orton et al., 2024).

In particular, interdisciplinary approaches, those that address both the medical needs of the infant and the developmental needs, have been shown to be the most effective (Stedall et al., 2022). These approaches integrate the expertise of pediatricians, neurologists, physical therapists, occupational therapists, and speech-language pathologists to provide a comprehensive treatment plan. A multi-disciplinary strategy can more effectively support the diverse needs of preterm infants, leading to improved neurodevelopmental outcomes and better long-term quality of life.

Furthermore, the benefits of early intervention extend beyond just direct cognitive improvements. Research suggests that such interventions can also positively influence emotional regulation, social development, and behavior, contributing to an overall enhancement in the quality of life for preterm infants (Dell'Aversana et al., 2023). By promoting the development of these foundational skills early on, infants are better positioned to overcome the challenges posed by preterm birth and the neurological disruptions caused by seizures, leading to better neurocognitive outcomes in the long run (Camerota et al., 2023).

Use of Antiseizure Medications

Antiseizure Medications (ASMs) are widely used for epilepsy management, but their effects on cognitive development must be carefully considered. While effective seizure control is essential to prevent further neural damage, some ASMs have been associated with adverse cognitive effects, such as sedation, reduced processing speed, and impaired memory (Besag & Vasey, 2021; Novak et al., 2022). The choice of ASMs, dosing, and duration of treatment should be tailored to minimize these risks while ensuring optimal seizure management. Recent advances in pharmacogenomics hold promise for identifying personalized treatment strategies that reduce cognitive side effects (Aldenkamp et al., 2016).

Conclusion

Prematurity, accompanied by epilepsy as a comorbid condition, represents a critical area of research interest in neonatology with direct applications to clinical practice. This review highlights the often life-threatening challenges faced by preterm neonates, from the moment of birth to the later impact on their cognitive functioning.

The vulnerability of the immature brain to various factors, such as seizures, neuroinflammation, hypoxic-ischemic events, and underdeveloped neural structures, underscores the priority of early diagnosis for timely intervention. By identifying the nature of epileptic syndromes, multidisciplinary teams can design therapeutic strategies during the neonatal period. These strategies aim to both minimize adverse effects that hinder neonatal development and prevent potential deficits in memory, attention, and learning later in life. Advancements in neuroimaging, continuous EEG monitoring, and tailored therapeutic approaches provide promising pathways for improving outcomes. However, the variability in cognitive impacts across domains such as memory, attention, and executive functioning necessitates further research into specific therapeutic approaches.

Future research should aim to expand our understanding of the mechanisms linking prematurity, epilepsy, and cognitive outcomes. Longitudinal studies exploring the interplay of genetic, metabolic, and environmental factors are essential to developing innovative interventions. Ultimately, a comprehensive approach that combines early diagnosis, individualized care, and supportive therapies offers the greatest potential for optimizing the developmental trajectories of preterm neonates with epilepsy.

Conflict of Interest and originality of work

The authors declare the current work is free from plagiarism and there is no conflict of interest to it

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