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**REVIEW ARTICLE**

# Main Disorders of Cerebral Organization in Preterm Neonates

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## ABSTRACT

**Introduction:** central nervous system development in preterm neonates is a complex process, ranging from neuroectodermal induction to myelination. Both genetic and environmental factors influence this development, and any disruption may lead to disorders of cerebral organization.
**Objective:** to provide an updated overview of the main disorders of cerebral organization in preterm neonates.
**Methods:** a documentary review was conducted, selecting 30 relevant studies from databases including Medline, Virtual Health Library, SciELO, digital books, and Google Scholar. The selected publications, spanning from 1999 to 2024, specifically addressed cerebral organization disorders in preterm neonates.
**Results:** cerebral organization disorders include conditions such as encephalopathy of prematurity, idiopathic intellectual disability, autism spectrum disorders, focal cortical dysplasia, lissencephaly, and polymicrogyria, among others. Preterm neonates are at higher risk of developing these disorders due to central nervous system immaturity at birth. Various neuroprotective strategies have been developed.
**Conclusions:** preterm neonates are at significant risk of diverse neurological disorders due to cerebral immaturity at birth. Comprehensive, multidisciplinary care is essential to improve management and long-term outcomes. Early and appropriate intervention is crucial to minimize neurodevelopmental sequelae, and neuroprotective strategies are vital to enhancing these patients' quality of life.

**Keywords:** Cerebrum; Nervous System Diseases; Infant, Premature; Neurodevelopmental Disorders.

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## INTRODUCTION

Normal development of the central nervous system involves several essential stages: neuroectodermal induction, neurulation, neuronal proliferation and migration, apoptosis, neurogenesis and elimination of excess neurons, synaptogenesis, synaptic stabilization and pruning, gliogenesis, and myelination. These processes are governed by specific genes that regulate neural tube formation, neuronal cell division, neuronal size and morphology, programmed cell death, neuroglial interactions, and synaptic stabilization.[1]

Key events in human brain development occur within defined temporal windows: primary neurulation takes place between gestational weeks 3–4; prosencephalic development occurs from months 2–3 of gestation; neuronal proliferation peaks between months 3–4; neuronal migration spans months 3–5; cerebral organization begins around month 5 and continues for several years postnatally; and myelination starts at birth and extends into later childhood.[2]

Neurodevelopment, cognition, and behavior are complex biological processes with a predetermined genetic component that are simultaneously highly modulated by environmental influences. Genetic and environmental factors dynamically interact, with epigenetic mechanisms acting at their interface to regulate gene expression in response to internal and external conditions, developmental stage, tissue type, and cell lineage.[3]

Critical features of cerebral organizational development include: establishment and differentiation of subplate neurons; proper alignment, orientation, and laminar stratification of cortical neurons; gyral formation; elaboration of dendritic and axonal arborizations; formation of synaptic contacts; selective neuronal and synaptic pruning; and glial proliferation and differentiation. These events are particularly significant as they lay the foundation for the complex neural circuitry that characterizes the human brain and prepare the substrate for the final developmental milestone—myelination.[4]

Genetic–environmental interactions begin at conception, influencing the mother–placenta–fetus triad, with short- and long-term effects on neonatal and childhood brain development. Developmental neuroplasticity is most pronounced during critical and sensitive periods of brain maturation, especially within the first 1,000 days of life. Maladaptive interactions within the triad—such as maternal immune activation—can impair progenitor neuronal and glial populations in transient embryonic and fetal brain structures. Later in gestation, destructive fetal brain injuries often result from placental ischemic syndromes linked to major obstetric complications.[5]

Disruptions in the sequence of events underlying cerebral organization give rise to various disorders, with preterm neonates constituting a high-risk population. Subplate neuronal pathology has been implicated in multiple conditions, including encephalopathy of prematurity. Abnormalities in gyral and/or lobar development are observed in idiopathic intellectual disability and autism spectrum disorder. Axonal developmental impairment occurs across a range of pediatric central and peripheral nervous system disorders, resulting in a broad spectrum of clinical disabilities.[4]

Globally, preterm birth affects 15 million newborns annually. It is the leading cause of death in children under 5 years of age, accounting for approximately 1 million deaths each year. Among survivors, preterm birth is the primary cause of disability-adjusted life years due to neurological injury and long-term neurodevelopmental sequelae.[6]

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Given the magnitude of this public health challenge and its profound implications for individuals, families, society, and health systems, this article aims to provide an updated synthesis of current knowledge on the main disorders of cerebral organization in preterm neonates.

## METHODS

An exhaustive documentary review was carried out. Relevant studies were identified and selected from electronic databases including Medline, the Virtual Health Library, SciELO, digital books and book chapters, as well as through the Google Scholar search engine. Search terms included *fetal brain development*, *neurodevelopment*, and *cerebral organization disorders*. A total of 89 publications from 1999 to 2024 were retrieved, written in Spanish, English, French, and Portuguese. From these, 30 studies were selected based on relevance, methodological quality, and specific focus on cerebral organization disorders in preterm neonates.

## DEVELOPMENT

### Phases of Cerebral Development

The main phases of cerebral development can be summarized as follows: neuroectodermal induction, neural tube formation, followed by telencephalic development, neurogenesis (production of germinal neurons and subsequently mature neurons), neuronal migration, programmed neuronal death, neurite outgrowth (axons and dendrites), elimination of superfluous neurites, synaptogenesis, selective synaptic pruning and stabilization, angiogenesis, gliogenesis (generation of astrocytes and oligodendrocytes), and myelination.[7]

These processes are commonly grouped into four developmental periods:

- Proliferation (gestational weeks [GW] 1–7),
- Migration (GW 8–15),
- Differentiation (GW 16–26), and
- Maturation (from GW 27 through adulthood).[1]

The general architecture of the human brain is largely established during the first six months of fetal life, driven predominantly by strong genetic influences. The relative weight of these genetic factors diminishes during the third trimester of gestation, when environmental factors become increasingly critical—particularly in shaping the final stages of prenatal and early postnatal brain development. Thus, human brain development is a highly complex, orchestrated process that lays the foundation for lifelong cognition, behavior, and emotional regulation.[8] Epigenetic mechanisms are also presumed to play a key role. Disruption of any developmental phase may lead to impaired brain growth and/or structural malformations.[7]

During the third trimester, long-chain polyunsaturated fatty acids (LC-PUFAs) increase substantially in fetal circulation, with a process of "biomagnification" observed in the fetal brain. Reduced availability of arachidonic acid, for example, may lead to altered brain development—including reduced neuronal proliferation and atrophy of the cerebral cortex and hippocampus.[9]

Both preterm and term newborns are in an active phase of brain development. Key processes occurring during the third trimester include the completion of neuronal migration, programmed cell death, axonal and dendritic outgrowth, and the initial wave of synaptogenesis.[7]

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From the fifth month of gestation onward, cerebral organization accelerates and continues for several years after birth. During this period, there is extensive dendritic arborization, formation of numerous synaptic connections, layering and orientation of neurons and their processes (cytoarchitecture), programmed cell death (apoptosis), and cellular differentiation and specialization. These events unfold under the influence of neurotrophic factors and their interaction with external stimuli.[4] Preterm neonates are born during this highly active phase of cerebral organization, rendering them particularly vulnerable to a range of developmental brain disorders.

**Disorders of Cerebral Organization**

Cerebral organization disorders are classified into seven categories:

1. Subcortical neuron disorders
2. Lamination disorders
3. Gyration (gyrification) disorders
4. Dendritic and synaptogenesis disorders
5. Axonal growth disorders
6. Glial proliferation and differentiation disorders
7. Disorders involving multiple organizational events, delineated *in vivo*, including those linked to prematurity, nutritional factors, and experiential influences.[4]

As detailed below, many of these conditions involve disruptions across more than one developmental process.

**Subcortical Neuron Disorders**

This group includes encephalopathy of prematurity, epilepsy, autism, and schizophrenia.[4] This review focuses specifically on encephalopathy of prematurity—a multifactorial nosological entity encompassing a spectrum of neurodevelopmental disorders, along with characteristic neuropathological and neuroimaging findings associated with preterm birth. Its pathogenesis involves not only destructive processes but also disturbances in brain maturation itself. The underlying substrate is impaired development of the immature brain due to premature birth, with brain injury extending beyond the neonatal period; therefore, it should be regarded as a chronic health condition rather than solely a disability.[10]

Neuropathological features of encephalopathy of prematurity are divided into two main groups:

- Group I: White matter injury, expressed as periventricular leukomalacia (PVL), characterized by focal white matter necrosis, diffuse gliosis, and microglial activation. It also includes acute, diffuse loss of pre-oligodendrocytes (pre-OLs), oxidative and nitrosative stress markers in pre-OLs, impaired pre-OL maturation despite attempted repopulation, and upregulation of excitatory amino acid transporters, inducible nitric oxide synthase (iNOS) in astrocytes and microglia, and immunopositive astrocyte responses.
- Group II: Gray matter injury, featuring neuronal loss and/or gliosis in variable combinations involving the thalamus, basal ganglia, hippocampus, and cerebellar dentate nucleus; deficits in interstitial neurons and reduced GABAergic neurons in cerebral white matter; and focal or diffuse periventricular axonal injury.[11]

It is increasingly evident that encephalopathy of prematurity also entails maturational disturbances affecting not only white matter developmental targets but also gray matter maturation. This expanded perspective has been driven in part by the broad clinical phenotypes observed in modern preterm survivors—phenotypes that cannot be explained by white matter injury alone. The pathogenesis of cerebral white matter injury in this condition involves a tightly interrelated set of factors: periventricular vascular anatomy and physiology, cerebral ischemia,

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impaired cerebrovascular autoregulation (leading to passive, pressure-dependent cerebral blood flow), and, critically, infection and inflammation—particularly the synergistic potentiation between ischemia and inflammatory processes.[12]

Preterm neonates with periventricular white matter lesions may experience destruction of subplate neurons—a transient developmental structure appearing around gestational week 10 that serves as a "waiting zone" for thalamocortical axons before they invade the neocortical plate to reach cortical layer IV, essential for proper thalamocortical connectivity. Subplate neuron loss may contribute to thalamocortical connectivity abnormalities recently demonstrated via MRI in preterm infants, as well as to associated cognitive and/or motor impairments.[7]

The main clinical contexts of encephalopathy of prematurity fall into two categories:
1. Hypoxia–ischemia–related: fetal metabolic acidosis, respiratory failure secondary to severe respiratory distress syndrome, cardiac failure and/or hypotension, severe respiratory disease, recurrent apnea, significant patent ductus arteriosus, congenital heart disease, and sepsis.
2. Systemic inflammation–related: maternal intrauterine infection, neonatal sepsis, and necrotizing enterocolitis.[13]

In clinical practice, neonatologists often focus on managing the multiple, life-threatening complications affecting extremely preterm neonates. Consequently, comprehensive neurodevelopmental assessments—including evaluation of primary or secondary neurological injury resulting from concurrent morbidities or necessary diagnostic and therapeutic interventions—are frequently overlooked.

**Lamination Disorders**

Lamination refers to the proper alignment, orientation, and stratification of cortical neurons. Many underlying cortical malformations—such as epilepsy, cerebral palsy, global intellectual disability, and neuropsychiatric disorders—exhibit aberrant laminar patterns. Key conditions in this category include focal cortical dysplasia, lissencephaly, and polymicrogyria.[4]

Focal cortical dysplasia (FCD) is characterized by disrupted cortical lamination confined to a sharply demarcated cortical region. High-resolution brain MRI occasionally reveals such focal areas in patients with drug-resistant epilepsy.[14]

Currently, the International League Against Epilepsy (ILAE) classifies FCD into three main types, with further subtypes:

- Type I: Features dislamination and disrupted tissue architecture, with morphologically normal neurons and glial cells. Subtypes include radial abnormalities (Ia), abnormal horizontal lamination (Ib), and a combination of both (Ic).
- Type II: Defined by dysplastic megalocytic neurons intermixed with normal neurons. Subtypes include dysmorphic neurons alone (IIa) and dysmorphic neurons plus balloon cells (IIb).
- Type III: Similar to Type I but occurs adjacent to another lesion. Subtypes include hippocampal sclerosis (IIIa), glial tumors (IIIb), vascular malformations (IIIc), and other acquired lesions (IIId).[15]

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The clinical spectrum of FCD is broad, encompassing febrile seizure history and drug-refractory epilepsy with seizure types ranging from focal to generalized—such as tonic, absence, generalized tonic-clonic, myoclonic, and clonic seizures. Cognitive decline and psychiatric disorders may also occur; a minority of patients remain asymptomatic. MRI findings include cortical thickening, blurred gray–white matter junction, the transmantle sign, and/or abnormal gyral/sulcal patterns.[16]

Preterm neonates are at increased risk of developing FCD due to central nervous system immaturity at birth.
Lissencephaly is marked by cortical thickening and abnormal gyral patterns, ranging from complete absence of gyri (agyria) to abnormally broad gyri (pachygyria). It is classified into Type 1 (classical lissencephaly) and Type 2 (cobblestone lissencephaly), though Type 2 is often excluded due to distinct pathophysiology. Modern classification emphasizes severity, cortical thickening, gyral abnormality gradient, and association with other malformations. Clinically, two forms exist:

- Complete: presents with seizures and global developmental delay.
- Incomplete: features hypotonia, microcephaly, or facial dysmorphisms.

Seizures typically begin within the first month of life and may include epileptic spasms, myoclonus, or tonic seizures. Key associated genes include *LIS1*, *RELN*, and *DCX*.[17]

Polymicrogyria is characterized by an excessive number of small, abnormally formed gyri separated by shallow, thickened sulci.[15] It is one of the most common cortical malformations, resulting from embryological and genetic disruptions. It affects the cerebral cortex—a structure essential for sensory, motor, and cognitive functions. Notably, mutations in the *GRIN1* gene, which encodes the GluN1 subunit of the NMDA receptor (critical for neuroplasticity), have been implicated.[18] Clinical manifestations depend on the extent and etiology of cortical involvement, typically presenting with moderate-to-severe developmental delay and significant motor dysfunction, including hemiparesis or tetraparesia. Drug-resistant epilepsy—featuring complex partial or multiple generalized seizures—may emerge beyond the neonatal period.[19]

**Gyration Abnormalities**

Abnormal cortical gyration encompasses a spectrum of genetic and acquired malformations, including pachygyria (already discussed under lissencephaly), lissencephaly, and polymicrogyria. Additional anomalies involve maldevelopment of individual or lobular gyri; for instance, an enlarged superior temporal gyrus is observed in Down syndrome.[4]

Pachygyria, as a distinct entity, results from abnormal neuronal migration during corticogenesis, leading to a smooth cerebral surface due to absent (agyria) or reduced and shallow gyri. Histologically, the cortex exhibits fewer than the normal six layers—typically four—causing cortical thickening and reduced white matter volume, reversing the normal white-to-gray matter ratio.[17]

Clinically, independent ambulation is delayed beyond age three. Patients may achieve sphincter control and develop rudimentary language based on isolated words for basic needs. They display generalized hypertonia (without severe contractures), alert gaze, microcephaly, and often refractory epilepsy with atonic, myoclonic, or complex partial seizures.[20]

Conditions such as lissencephaly, polymicrogyria, and pachygyria are associated with prematurity, as preterm infants are at higher risk of cerebral malformations due to neurodevelopmental immaturity at birth. These disorders frequently manifest as drug-resistant epilepsy, and while determining exact etiology remains challenging, a comprehensive, multidisciplinary approach can improve diagnostic yield and clinical management.

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**Dendritic and Synaptogenesis Disorders**
This category includes idiopathic intellectual disability (with or without seizures), autism spectrum disorder (ASD), Rett syndrome, fragile X syndrome, and Down syndrome.[4] This review focuses on the first two.

Idiopathic intellectual disability refers to a group of disorders characterized by deficits in intellectual and adaptive functioning, with onset before maturity. Core impairments include reasoning, learning, problem-solving, social skills, and adaptive behavior.[21] Most affected infants lack significant neonatal morbidities.

Clinical and imaging data suggest that the primary pathology involves disrupted maturation of cerebral cortical neurons, particularly during the final weeks of gestation—a period of exceptionally rapid cortical development corresponding to late preterm birth. Impaired cortical maturation in late preterm infants represents a form of primary neuronal dysmaturation, previously documented in extremely and very preterm infants through experimental and clinical studies.[22]

While prematurity is a general risk factor for intellectual disability, its specific link to *idiopathic* forms is complex and likely multifactorial.

Autism spectrum disorder (ASD) is a neurobiological condition emerging in early childhood, marked by impairments in social communication and interaction, alongside restricted, repetitive behaviors. Its etiology is thought to stem from disrupted neural connectivity, primarily driven by genetic variants affecting early brain development. Neuroimaging and animal models show altered brain volume and neuronal density in limbic structures, the cerebellum, and frontotemporal regions.[23] Prematurity is recognized as a significant risk factor for ASD.[24]

Early recognition of ASD signs in preterm children by healthcare teams, families, and educators is crucial for timely intervention.

**Axonal Injury**
Axonal injury may be a primary event in cerebral white matter damage. While focal necrosis shows obvious axonal disruption, premyelinating axons in preterm white matter are rapidly developing and likely highly vulnerable—even in areas distant from necrotic foci. Diffuse axonal degeneration has been detected in the widespread component of periventricular leukomalacia (PVL) via immunostaining. It remains unclear whether this is a primary injury or a secondary phenomenon. If primary, expected developmental consequences include hypomyelination (due to failed axonal ensheathment by pre-oligodendrocytes and loss of axon–oligodendroglial trophic interactions) and reduced cortical and thalamic/basal ganglia volumes (via anterograde and retrograde degeneration)—patterns consistently observed in preterm survivors.[11]

As previously noted, axonal injury is an integral component of encephalopathy of prematurity. The spatiotemporal pattern of brain connectivity development suggests that sensorimotor and behavioral impairments arise during early prematurity, as thalamocortical and limbic pathways mature first—creating an early vulnerability window. In contrast, significant cognitive deficits likely result from damage to associative corticocortical connectivity, which develops in later stages of prematurity. Future research must integrate MRI, neuroanatomical metrics, and genomic data to enable early diagnosis, predict neurodevelopmental deficits, time rehabilitation interventions appropriately, and support longitudinal follow-up of preterm children. Such integrated approaches will advance the conceptual framework of "connectivity disorders"—including cerebral palsy, schizophrenia, and autism.[25]

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This field demands significant technological advances to achieve diagnostic precision and ensure timely, effective rehabilitation for affected individuals.

**Glial Proliferation and Differentiation Disorders**

Glial cells are fundamental to brain development, and disruption of their normal developmental processes—particularly "immune activation"—contributes significantly to brain injury in preterm neonates.[26]

The primary non-hemorrhagic white matter injury in preterm infants is periventricular leukomalacia (PVL), which encompasses cystic or non-cystic necrotic lesions of varying sizes, typically located in periventricular regions but also found in the internal capsule and corpus callosum. These lesions are surrounded by diffuse white matter gliosis and microglial activation. Importantly, diffuse gliosis and microglial reaction often occur even in the absence of focal necrosis. Neuronal loss in the cerebral cortex, hippocampus, and deep nuclear structures is commonly associated with PVL. In non-cystic white matter injury, there is a reduction in late-maturing interneurons. In the diffuse component, pre-oligodendrocytes (pre-OLs) degenerate and proliferate but fail to mature, resulting in hypomyelination accompanied by gliosis and microgliosis. The vulnerability of subplate neurons and axons—exacerbated by gliosis and microglial activation—may disrupt normal cortical and thalamic development.[27]

Laboratory evidence supports the hypothesis that microglia play a central role in the pathogenesis of these lesions. During normal brain development, microglia actively participate in physiological synaptic and neuritic remodeling. However, it remains unclear how the fetal inflammatory response syndrome—known to activate microglia—interferes with these essential developmental processes.[7]

Clinically, preterm infants with white matter injury exhibit a variable presentation depending on lesion severity and location. Common manifestations include impairments in cognition, motor development, neurosensory function, and language.[27]

Further research is urgently needed to clarify the pathophysiological role of microglial dysfunction in preterm brain injury, as these mechanisms may profoundly impact long-term neurodevelopment and quality of life, necessitating careful follow-up and targeted interventions.

**Myelination Disorders**

Abnormal myelination is a hallmark of chronic white matter injury. Myelination begins in the preterm brain and normally follows well-defined spatiotemporal sequences that continue for years after birth. Myelin's primary function is to insulate axons, ensuring optimal nerve conduction throughout the central nervous system. Beyond conduction, myelin sheaths are dynamic structures that actively contribute to learning and memory; adaptive changes in myelin thickness can strengthen or weaken the relative efficiency of neural signaling. This myelin plasticity represents a mechanism by which the nervous system can modulate information flow along competing pathways to optimize new learning.[28]

Three main mechanisms underlie myelination disorders:

1. Arrested or abnormal development of oligodendrocyte precursors, preventing the formation of mature, myelin basic protein–producing oligodendrocytes;
2. Oligodendroglial dysfunction leading to myelin breakdown; and
3. Primary axonal disorders causing aberrant signaling and impaired trophic interactions with developing oligodendrocytes, resulting in defective myelination and/or myelin maintenance.[29]

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While myelination deficits occur across many neurodevelopmental conditions, they are the dominant neuropathological feature only in specific entities—such as cerebral white matter hypoplasia—and are strongly associated with prematurity, nutritional factors (e.g., malnutrition, iron or zinc deficiency, breastfeeding patterns), and experiential influences. This review focuses exclusively on prematurity-related factors.

Emerging understanding of myelin's active role underscores the profound impact that white matter injury can have on disrupting the timing and sequence of myelination during critical developmental windows in preterm infants. This process intersects with late neurogenesis, gliogenesis, neuronal and glial maturation, synaptogenesis, and myelination itself. Aberrant myelination likely affects both gray and white matter, leading to enduring disruptions in the final architecture and connectivity of neural networks essential for normal brain function.[29]

Surviving preterm neonates often present with a constellation of motor, cognitive, and behavioral disabilities. These are linked not only to severe, focal injuries (which are relatively rare) but more commonly to moderate, diffuse disturbances in cellular maturation.[6,28] Myelination abnormalities in preterm infants significantly contribute to these long-term neurodevelopmental impairments.

**Neuroprotective Strategies for the Preterm Neonate**

Current and emerging neuroprotective approaches include:

- Antenatal corticosteroids: reduce preterm mortality, respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis.
- Antenatal magnesium sulfate: lowers the risk of cerebral palsy and improves gross motor function.
- Delayed cord clamping (>30 seconds): may reduce intraventricular hemorrhage by up to 50 %.
- Caffeine therapy: decreases apnea, need for mechanical ventilation, and the combined risk of mortality or survival with cerebral palsy, cognitive deficit, blindness, or deafness in neonates weighing 500–1250 g at birth.
- Erythropoietin: exerts anti-inflammatory, anti-excitotoxic, antioxidant, and anti-apoptotic effects while promoting neurogenesis, oligodendrogenesis, and angiogenesis.
- Melatonin: a potent antioxidant that scavenges free radicals and upregulates endogenous antioxidant enzymes (e.g., glutathione, glutathione reductase, peroxidase, superoxide dismutase).
- Stem cell therapy: currently under investigation in clinical trials.

Optimal neuroprotection will likely require multimodal interventions applied at strategic developmental timepoints.[30]

These strategies are crucial for reducing the incidence of cerebral palsy, improving motor outcomes, and mitigating severe complications—thereby fostering healthier neurodevelopment in preterm infants.

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## CONCLUSIONS

Preterm neonates are vulnerable to a wide spectrum of cerebral organization disorders due to brain immaturity at birth. These disturbances affect multiple developmental domains—including subcortical neurons, cortical lamination, gyration, dendritic arborization, synaptogenesis, axonal growth, glial proliferation and differentiation, and integrated organizational events—where prematurity-related factors play a pivotal role. These disorders may arise from neurological, genetic, or environmental influences and often involve overlapping disruptions across several developmental phases. Key conditions include, among others: encephalopathy of prematurity, focal cortical dysplasia, lissencephaly, polymicrogyria, pachygyria, idiopathic intellectual disability, and autism spectrum disorder. Their clinical manifestations are highly heterogeneous, encompassing global developmental delay, motor impairments, communication difficulties, epilepsy, physical anomalies, repetitive behaviors, and attention deficits. Given the profound and lasting impact of these disorders, early identification, multidisciplinary follow-up, and implementation of neuroprotective strategies are essential to improving long-term outcomes and quality of life for preterm infants.

**Conflict of Interest**
The author declares no conflict of interest.

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