Review

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Review

Emerging Mitochondrial Perspectives and Potential Therapeutics in Genetic Developmental and Epileptic Encephalopathy (DEE)

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Abstract

Developmental and Epileptic Encephalopathies (DEEs) comprise a heterogeneous group of severe neurological disorders with early onset refractory epilepsy and profound neurodevelopmental impairments. Despite the availability of more than thirty anti-seizure medications, most individuals with DEE remain refractory, experiencing persistent seizures that impose substantial burdens on patients, caregivers, and health care systems. DEEs are predominantly genetic, largely caused by de novo mutations, although non-genetic factors also contribute. Crucially, developmental deficits in DEE arise from both the underlying etiology and the disruptive effects of epileptic activity on the developing brain, distinguishing DEE from epilepsies without major neurodevelopmental involvement. Seizures during critical developmental windows exert acute and enduring effects on neurogenesis, synaptogenesis, circuit refinement, pruning, and brain maturation, which can greatly disrupt neurodevelopment. Mitochondria emerge as central regulators at the intersection of neurodevelopment and epilepsy. Mitochondrial dysfunction, whether from primary genetic mutations or seizure-induced injury, impairs bioenergetics, calcium homeostasis, redox states, and metabolic signaling, lowers seizure thresholds, and increases neuronal vulnerability. Moreover, mitochondrial metabolism directly interfaces with epigenetic regulation, linking energy state to long-term gene expression, altering developmental programming. This review synthesizes current knowledge on mitochondrial contributions to DEE pathogenesis, clinical diagnosis, and highlights emerging mitochondrial-targeted therapeutic strategies.

Keywords: Developmental and Epileptic Encephalopathy (DEE); epilepsy; mitochondria; neuroimaging; neurodevelopment

1. Introduction

Developmental and Epileptic Encephalopathy (DEE) is a heterogeneous group of severe neurological disorders that present in infancy or early childhood [1–5] with frequent, often drug-resistant seizures and significant developmental impairments [1,5–9]. The cumulative incidence of DEEs in children up to age 16 has been estimated at about 169 per 100,000 children [10]. DEE is distinguished clinically by the combination of early-onset epileptic seizures (multifocal, tonic-clonic, myoclonic, or spasms) and global neurodevelopmental delay or regression [11] involving cognitive,

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psychiatric, motor, and social domains [12]. Electroencephalographic (EEG) abnormalities are usually prominent. DEE are predominantly caused by genetic etiology [13]. More than 900 genes [7,14] have been identified for pathogenesis of DEE [1,6], mostly de novo mutations. In addition to genetic causes, non-genetic factors [15], such as infection, hypoxia, and immune abnormalities, can also contribute to DEE [16]. Although more than 30 anti-seizure medications (ASMs) [17] are now available in the U.S., most DEE patients are refractory, unresponsive to current ASMs [18] , continuing to have frequent uncontrolled seizures. In conjunction of co-morbidities from neurodevelopmental impairments, DEE impose a high disease burden for health care systems [19,20] and caregivers [21–24]. New intervention strategies targeting additional pathogenesis pathways are needed for DEE care [15,25].

Importantly, developmental impairments in DEE arise from both the underlying genetic cause itself and the impact of uncontrolled epileptic activity on brain maturation, making DEE more complex than classic epileptic syndromes without marked neurodevelopmental involvement as well as neurodevelopmental diseases without seizures. Abnormal neurodevelopment disrupts normal brain network formation during development [26–28]; for example, premature early branching of migrating neurons fail to reach their correct cortical layers, abnormal neuronal progenitors from correctly dividing or maturing, leading to an abnormal brain "cytoarchitecture" that cannot process signals normally, and aberrant synaptic vesicles, axonal or dendrite formations that can disrupt the balance between neuronal excitation and inhibition during critical stages of brain formation. These brain network wiring abnormalities create a pathological network that is hyperexcitable and prone to seizures [26–28]. Seizures exert both acute and long-lasting effects on neurodevelopment [29,30]. Seizures occurring during critical developmental stages can disrupt the brain's "pruning" processes, which are essential for normal maturation, leading to both immediate and long-lasting neurodevelopmental effects across lifespan [31]. During early life, neuronal activity is not merely permissive but instructive for neurodevelopment, guiding neurogenesis, neuronal migration, synaptogenesis, circuit refinement, and myelination. Pathological hypersynchronous activity associated with seizures can therefore derail these tightly regulated programs, leading to persistent alterations in brain structure and function. In DEE, a self-perpetuating pathogenic vicious cycle exists in which the underlying genetic or structural neurodevelopmental abnormality precipitates early seizures, and seizure activity in turn exacerbates injury to the developing brain, further amplifying neurodevelopmental impairment.

Despite expanding genetic insights, treatment remains challenging, as seizures are frequently refractory to standard antiseizure medications and developmental outcomes are often poor. Precision therapies, including gene-targeted approaches, pathway-specific drugs, dietary therapies, neuromodulation, and early intervention strategies, are emerging but remain limited.

Mitochondria are critical determinants of both neurodevelopment and epilepsy. In DEE, pathogenic contributions of mitochondrial dysfunction can arise both from primary mutations in mitochondrial DNA or nuclear-encoded mitochondrial genes as well as from indirect insults, like prolonged seizures, which disrupt mitochondrial integrity and dynamics. The bi-directional relationship [32–35] of primary mitochondrial diseases (PMD) and DEE is well recognized. As central metabolic and signaling organelles, mitochondria orchestrate bioenergetic and biosynthetic programs essential for neuronal birth, differentiation, migration, maturation and the establishment and refinement of synaptic networks [36]. Neurons are uniquely dependent on oxidative phosphorylation to meet the high energy demands of presynaptic and postsynaptic signaling, rendering them particularly sensitive to perturbations in mitochondrial metabolism and oxygen availability; this reliance extends to fundamental processes including broadly neurodevelopment [37], neurogenesis [38–40], and activity-dependent synaptic plasticity [41]. When mitochondrial function is compromised, deficits in energy shortage, chemical imbalance, dysregulation of calcium, redox, and metabolic signaling undermine neuronal homeostasis, make the brain more susceptible to spontaneous, uncontrolled electrical discharges, prone to seizures, thus lower seizure thresholds [42,43]. Importantly, mitochondrial genomes are tightly associated with epigenomes [44].

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Mitochondrial functions can regulate epigenetic modulation [44–47] affecting long-term gene expressions, thereby shaping developmental programming.

This review will summarize emerging roles of mitochondria in DEE pathogenesis, diagnosis, and potential therapeutic interventions. This review summarizes clinical and genetic etiology and heterogeneity in DEE, current clinical diagnosis for DEE with EEG and neuroimaging, convergence of mitochondrial functions in DEE and PMD, as well as mitochondria as potential therapeutic targets.

2. Clinical Heterogeneity of Developmental and Epileptic Encephalopathy (DEE)

Developmental and epileptic encephalopathies (DEEs) [1–5] comprise a highly heterogeneous group of neurodevelopmental disorders characterized by early-onset, often intractable, seizures accompanied by developmental delay or regression. Clinically, DEE encompasses a spectrum of syndromes such as infantile epileptic spasms syndrome (IESS/West syndrome), Dravet syndrome, Lennox–Gastaut syndrome, early infantile DEE (historically Ohtahara syndrome), and DEE with burst-suppression EEG. Epileptic activity contributes to, or is associated with, progressive impairment of cognitive, behavioral, and neurological development, beyond what would be expected from the underlying etiology alone. Affected individuals commonly exhibit intellectual disability, motor dysfunction, speech impairment, autism spectrum features, and behavioral abnormalities, with comorbidities that persist throughout life.

Clinical heterogeneity [48–51] in DEE is characterized by a vast spectrum of seizure types, varied ages of onset, and diverse neurodevelopmental outcomes that emerge from both genetic and non-genetic causes. Clinical presentations vary widely with respect to age at seizure onset—ranging from the neonatal period to early childhood—seizure types (including epileptic spasms, focal seizures, and tonic or myoclonic seizures), electroencephalographic patterns, and neurodevelopmental trajectories. Some individuals exhibit profound developmental impairment from birth, whereas others demonstrate an initial period of typical development followed by stagnation or regression coinciding with seizure onset. This variability reflects the diverse etiological landscape of DEEs, which includes monogenic mutations affecting ion channels, synaptic proteins, transcriptional regulators, and metabolic pathways, as well as acquired and structural causes. Phenotypic variability in genetic epilepsies is well-documented [48,52], where identical genetic variants can lead to vastly different clinical outcomes with markedly different seizure burdens, cognitive outcomes, and responses to treatment.

Beyond seizures and global developmental impairment, DEEs are associated with a broad spectrum of co-morbidities [1,21,48] that further contribute to their clinical heterogeneity. These include motor dysfunction, hypotonia or spasticity, movement disorders, visual and auditory impairments, sleep disturbances, gastrointestinal dysfunction, and neuropsychiatric features such as autism spectrum behaviors, anxiety, and impaired social communication. The severity and combination of these comorbidities differ substantially across DEE subtypes and individuals, underscoring that DEEs are multisystem neurodevelopmental disorders rather than seizure-only conditions. Importantly, seizure control does not uniformly predict developmental outcome, suggesting that both epileptic activity and the underlying genetic or molecular pathology independently shape clinical trajectories. This profound heterogeneity poses major challenges for diagnosis, prognosis, and therapeutic development, and highlights the need for precision medicine approaches that integrate genotype, developmental timing, and systems-level brain dysfunction.

3. Electroencephalogram (EEG) for Developmental and Epileptic Encephalopathy (DEE)

Electroencephalography (EEG) [4,49,53] is consistently abnormal in patients with DEE, reflecting profound disruptions in cortical network function characteristic of these disorders which may be evident from early infancy. Common EEG abnormalities include multifocal epileptiform discharges, chaotic background activity, burst-suppression in the neonatal period, and hypsarrhythmia in

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infantile spasms, with specific patterns often correlating with underlying syndromes and age of onset. Background slowing is a common feature, ranging from generalized to multifocal slowing, indicating impaired cortical networks. In many DEEs, interictal EEG may show high-voltage, chaotic patterns such as hypsarrhythmia, particularly in infantile spasms, with multifocal spikes superimposed on irregular slow waves. EEG may also demonstrate burst-suppression patterns, characterized by alternating periods of high-voltage bursts and near-flat suppression, typically observed in neonatal or early infantile DEE syndromes such as Ohtahara syndrome. These patterns reflect the severity of underlying structural or functional cortical disruption and often correlate with profound developmental delays.

3.1. General EEG Features in DEE:

EEG in DEE typically reflects severe, diffuse cortical dysfunction, which may be evident from early infancy. Background slowing is a common feature, ranging from generalized to multifocal slowing, indicating impaired cortical networks. In many DEEs, interictal EEG may show high-voltage, chaotic patterns such as hypsarrhythmia, particularly in infantile spasms, with multifocal spikes superimposed on irregular slow waves. EEG may also demonstrate burst-suppression patterns, characterized by alternating periods of high-voltage bursts and near-flat suppression, typically observed in neonatal or early infantile DEE syndromes such as Ohtahara syndrome. These patterns reflect the severity of underlying structural or functional cortical disruption and often correlate with profound developmental delays.

From a functional perspective, these EEG abnormalities are not only diagnostic but also prognostic. The persistence of severe patterns such as hypsarrhythmia or burst suppression is associated with worse neurodevelopmental outcomes, even if seizures are partially controlled. Additionally, EEG is critical in monitoring treatment response, as normalization or improvement of background and epileptiform activity often parallels clinical improvement. EEG abnormalities can evolve over time, with early neonatal patterns sometimes transitioning into more organized or syndrome-specific abnormalities in infancy or childhood.

3.2. Syndrome-Specific EEG Patterns:

EEG patterns in DEE [4,7,54] are often syndrome-specific and can provide critical diagnostic clues. For instance, West syndrome [55] presents EEG with hypsarrhythmia, a highly disorganized high-amplitude background with multifocal spikes and sharp waves, often associated with clinical infantile spasms and electrodecremental events. The hallmark EEG pattern in Lennox-Gastaut syndrome (LGS) [56] is characterized by slow spike-and-wave discharges (1.5–2.5 Hz) and generalized paroxysmal fast activity, reflecting the complex, multi-focal seizure types and cognitive impairment seen in these patients. In contrast to other DEEs, in the Dravet Syndrome [57,58], the early interictal EEG may be normal or only subtly abnormal, which is itself a diagnostic clue when paired with frequent febrile seizures, but typically evolves to generalized spike-wave activity and other abnormalities; background activity can deteriorate and bilateral asymmetric, focal, or multifocal polyspike-and-slow-wave paroxysms may appear. On the other hand, the Ohtahara syndrome [59–62] typically presents in the neonatal period with a burst-suppression EEG, showing high-voltage bursts alternating with suppression. Other genetic DEEs, such as CDKL5-related encephalopathy [63,64], often show multifocal spikes or hypsarrhythmia-like patterns in early infancy, correlating with severe developmental delays and early-onset seizures. STXBP1-related DEE frequently demonstrates multifocal or generalized epileptiform discharges with tonic and myoclonic seizures, reflecting widespread synaptic dysfunction. The syndrome-specific EEG phenotypes often evolve with age, emphasizing the need for serial EEG monitoring to guide treatment decisions and to inform prognosis. Recognizing these patterns can also suggest likely underlying genetic etiologies, facilitating targeted genetic testing.

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3.3. Functional and Prognostic Significance of EEG in DEE:

EEG [65–69] is a vital tool in the management of DEE, serving not only as a diagnostic modality but also as a functional biomarker of disease severity. While the causal mechanisms linking epileptiform discharges to developmental dysfunction remain complex, clinical evidence suggests that the burden and persistence of EEG abnormalities often parallel the severity of developmental deficits. From a functional perspective, these EEG abnormalities are not only diagnostic but also prognostic. The presence of abnormal EEG patterns such as hypsarrhythmia, burst-suppression, or generalized slow spike-and-wave often correlates with the degree of cognitive impairment and developmental delay. Persistent severe EEG abnormalities typically indicate ongoing epileptic activity that can contribute to encephalopathy, reinforcing the concept of epileptic encephalopathy, where the EEG abnormalities directly impair neurodevelopment.

These aberrant electrical activities are not merely epiphenomena of seizures but may actively interfere with normal neurodevelopmental processes, contributing to cognitive and motor impairments. Indeed, studies in KCNQ2-related DEE [70] demonstrate that early multifocal epileptiform abnormalities and disorganized EEG background correlate with poorer motor and adaptive outcomes, supporting a relationship between pathological EEG activity and developmental severity. Similarly, baseline EEG features in SYNGAP1-associated DEE [71] have been proposed as potential biomarkers for developmental trajectories.

EEG also helps identify subclinical seizure activity, which is common in DEE and may otherwise go unnoticed but still contributes to neurological deterioration. The persistence of severe patterns such as hypsarrhythmia or burst suppression is associated with worse neurodevelopmental outcomes, even if seizures are partially controlled. Additionally, EEG is critical in monitoring treatment response, as normalization or improvement of background and epileptiform activity often parallels clinical improvement. EEG abnormalities can evolve over time, with early neonatal patterns sometimes transitioning into more organized or syndrome-specific abnormalities in infancy or childhood.

4. Neuroimaging for Developmental and Epileptic Encephalopathy (DEE)

Neuroimaging [72–74] is a cornerstone in the evaluation and characterization of DEE, providing critical structural, metabolic, and functional insights that complement clinical and genetic assessments. Conventional and advanced magnetic resonance imaging (MRI) is first-line in DEE, capable of identifying malformations of cortical development, delayed or aberrant myelination, cerebral and cerebellar atrophy, and other structural abnormalities that may underlie or contribute to refractory seizures and neurodevelopmental impairment; notably, MRI may initially be normal, particularly early in the disease course, and repeat imaging can reveal progressive or evolving changes over time. Proton magnetic resonance spectroscopy (MRS) further augments structural MRI by quantifying brain metabolites, such as N-acetylaspartate, choline, creatine, glutamate and glutamine lactate, lipids, branched chain amino acids, glycine and myoinositol, enabling detection of neuronal dysfunction, altered energy metabolism, and neurotransmitter imbalance even when morphology appears unremarkable, thus offering valuable biochemical biomarkers in pediatric neurological and metabolic disorders including DEE. Positron emission tomography (PET), especially with ^18F-fluorodeoxyglucose (FDG), reveals regional hypometabolism or hypermetabolism that often extends beyond conventional MRI lesions, illuminating dysfunctional epileptogenic networks and aiding localization in medically refractory cases; hybrid PET/MRI platforms enhance diagnostic yield by co-registering metabolic and anatomic data in a single session. Technetium 99m HMPAO (Hexamethylpropyleneamine Oxime) or Tc 99m Ethyl Cysteinate dimer (ECD) ictal and interictal SPECT can measure regional cerebral blood flow and thereby help to identify the epileptogenic focus [75]. Together, multimodal neuroimaging underscores the paradigm that DEE reflects not only focal structural lesions but also widespread metabolic and network

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derangements, thereby improving diagnostic precision, informing prognosis, and guiding therapeutic strategies including surgical planning.

4.1. Magnetic Resonance Imaging (MRI) in DEE

Magnetic resonance imaging (MRI) plays a central role in the diagnostic evaluation of childhood epilepsy or infant spasm [76–79], DEE [80–83], and developmental delays [84,85], by identifying structural brain abnormalities, defining etiologic subgroups, and guiding prognosis. Conventional MRI is frequently abnormal in DEE, particularly in early-onset and severe forms, and may reveal cortical malformations (e.g., focal cortical dysplasia, polymicrogyria, lissencephaly), abnormalities of neuronal migration and gyration, hippocampal malformations, cerebellar hypoplasia, and callosal dysgenesis. In neonatal- and infantile-onset DEEs, MRI may also demonstrate acquired injuries such as hypoxic–ischemic damage, intracranial hemorrhage, or metabolic patterns of injury involving the basal ganglia and thalami. Importantly, a normal MRI does not exclude DEE, especially in genetically defined syndromes, but the presence of a lesion substantially increases diagnostic yield and may point toward specific molecular pathways or candidate genes. In an MRI study of 147 children with epilepsy [86], a 74% prevalence of structural abnormalities was found with MRI. It notes that, while global rates in various studies range from 12% to 53%, yields are significantly higher (up to 72%) when dedicated epilepsy protocols are used at tertiary centers. In an MRI study of children with developmental delay [84], the diagnostic yield with abnormal MRI findings was found to be in 68% cases, and higher yield was seen in patients presenting with developmental delay plus other symptoms, such as epilepsy.

However, diagnostic yields of MRI in DEE are variable. In other DEE studies, MRI was normal in 66% of the cases [81]. For broader pediatric and adult epilepsy, which includes DEE phenotypes, between 44% and 82% of patients may show no abnormalities on standard 1.5 T or 3 T MRI scans [87]. For these negative cases with standard structural MRI, advanced MRI techniques further extend the value of neuroimaging in DEE by detecting subtle or evolving abnormalities not visible on standard sequences. High-resolution epilepsy MRI protocols [88], such as thin-slice T_1- and T_2-weighted imaging and FLAIR [89] and the harmonized neuroimaging of epilepsy structural sequences (HARNESS) epilepsy MRI protocol [90,91], may improve detection of focal cortical dysplasia [92] and hippocampal pathology, which may be relevant for surgical consideration even in the context of global developmental impairment.

For patients that do not show overt dysplasia or lesions with conventional anatomical MRI, diffusion tensor imaging (DTI) [93,94] can reveal widespread disruptions in white matter microstructure and network connectivity, supporting the concept that DEE is a disorder of aberrant neurodevelopmental axonal connectivity rather than solely focal pathology. Diffusion MRI [95–103] leverages anisotropic water diffusion properties in the biological tissue to generate MRI contrast [104,105], providing a non-invasive way to map white matter connections. In neuronal fibers, water molecules can readily diffuse along neuronal fiber orientation but are very limited perpendicular to the neuronal fiber orientation due to diffusion barriers of cell membranes and myeline sheath [106–109], allowing non-invasive mapping of neuronal track orientations and connections in the brain. In addition, diffusion MRI is sensitive to micro-environment in the brain, thus can provide a non-invasive way to probe the pathophysiological and neurodevelopmental features in live brains, such as neuroinflammation, demyelination, axonal injury, traumatic injury, or infections. Age-dependent changes in quantitative diffusivity during neurodevelopment are well recognized [110–112]. Developing brains rapidly change axonal characteristics in axonal density, axonal caliber, and myelination [110–112]. Diffusive parameters can be used to characterize brain maturation in pre-term infants [113–116], which showed gestation-age dependent and brain-region specific changes. Children with dyslexia [117–119] showed changes in these diffusivity parameters. Thus, quantitative diffusivity are increasingly used as biomarkers for white matter for neurodevelopment [110–112], brain maturation [113–116], cognitive abilities [117–119], brain injury [120–124], and

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neurodegeneration [125–128]. It may provide added values in diagnosis and prognosis for DEE with negative standard anatomical MRI.

Longitudinal MRI studies also demonstrate progressive changes in some DEEs, including cerebral or cerebellar atrophy, emphasizing that structural abnormalities may emerge over time and warrant repeat imaging. Collectively, MRI provides essential anatomical and developmental context in DEE, complements genetic and electrophysiologic data, and remains a cornerstone for phenotypic stratification and mechanistic insight.

4.2. Magnetic Resonance Spectroscopy (MRS) in DEE

Proton ^{1}H-magnetic resonance spectroscopy (MRS) is a non-invasive modality that quantifies brain metabolites *in vivo*, providing biochemical information that complements structural MRI and EEG in both epilepsy and developmental encephalopathy. In temporal lobe epilepsy patients that had negative structural MRI, ^{1}H-MRS could sensitively detect changes in hippocampi ipsilateral to the seizure side [129]. In epilepsy, ^{1}H-MRS [130] shows reduced N-acetylaspartate (NAA) and decreased NAA/creatine (Cr) or NAA/choline (Cho) ratios in epileptogenic regions such as the hippocampus even when conventional MRI is normal, reflecting neuronal loss or dysfunction and assisting with lateralization and localization in temporal lobe and other focal epilepsies. Elevated choline and myo-inositol can indicate gliosis or membrane turnover, while transient lactate peaks may be observed peri-ictally or post-seizure, further characterizing metabolic perturbations associated with seizure activity. These metabolite alterations have been documented in both structural MRI-negative temporal lobe epilepsy and malformations of cortical development, underscoring the value of ^{1}H-MRS in detecting metabolic abnormalities beyond what standard imaging reveals.

In developmental encephalopathies [131–134], particularly neonatal hypoxic-ischemic encephalopathy (HIE) [133] and childhood neurometabolic disorders [134], ^{1}H-MRS provides powerful prognostic and diagnostic biomarkers. Term and preterm neonates with HIE typically demonstrate elevated lactate and reduced NAA, with ratios such as NAA/Cr, lactate/Cho, and myo-inositol/NAA strongly correlating with long-term neurodevelopmental outcome and cerebral injury severity; these associations remain significant even when accounting for therapeutic hypothermia. Inborn errors of metabolism and other pediatric encephalopathies likewise exhibit distinctive spectroscopic patterns — for example, altered peaks for glycine in non-ketotic hyperglycinemia or persistent lactate in mitochondrial disorders — enabling identification of metabolic crises and monitoring of treatment effects. Thus, ^{1}H-MRS may serve as a critical adjunct in characterizing the biochemical underpinnings of developmental brain disorders and in risk stratification where conventional anatomical imaging may be insensitive.

4.3. Positron Emission Tomography (PET) in DEE

Positron emission tomography (PET) is a quantitative molecular imaging modality that enables in vivo visualization and measurement of biochemical, metabolic, and signaling processes in the living brain. PET relies on radiolabeled tracers—most commonly positron-emitting isotopes such as ^{18}F, ^{11}C, or ^{15}O—that are incorporated into biologically active molecules (e.g., glucose analogs, neurotransmitter ligands, or metabolic substrates). Following tracer administration, positron–electron annihilation events generate pairs of γ-photons detected in coincidence, allowing tomographic reconstruction of tracer distribution with high sensitivity. Unlike structural imaging techniques, PET provides direct functional readouts of cerebral glucose metabolism, blood flow, receptor density, neurotransmitter release, and neuroinflammatory activity, thereby linking cellular and molecular dynamics to system-level brain function. When integrated with MRI or CT, PET offers a powerful multimodal framework to map structure–function relationships and to interrogate disease-specific pathophysiology across development and neurological disorders.

In DEE, PET imaging—especially with ^{18}F-FDG (fluorodeoxyglucose) [135–140] can serve as a critical functional neuroimaging modality that complements conventional structural MRI and EEG.

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DEE refers to a group of severe, often genetically driven epileptic syndromes that begin in infancy or early childhood and are characterized by frequent, drug-resistant seizures as well as global developmental impairment. Clinical guidelines for DEE evaluation recommend PET to assist with syndrome classification and elucidate brain metabolic abnormalities that may not be apparent on MRI alone. PET can reveal regional hypometabolism or focal metabolic defects associated with epileptogenic zones in conditions like infantile epileptic spasms syndrome (a DEE subtype), West syndrome, or Lennox-Gastaut spectrum disorders, thus providing key data for diagnostic clarification and potential surgical planning in refractory cases when MRI is non-lesional. Thus, PET is incorporated into the diagnostic algorithm in select DEE cases to improve understanding of functional brain abnormalities and guide individualized clinical decision-making.

5. Genetic Heterogeneity of Developmental and Epileptic Encephalopathy (DEE)

The underlying genetic etiology [1,4,7,13,14,141–144] is a major contributor to disease causation of DEE. Pathogenic variants [28,144–147] are found in >50% of DEE patients using next-generation sequencing (NGS) [148–151]. Targeted Gene Panels, focusing on a pre-selected set of genes (often 100–400+) known to cause epilepsy, offer high depth of coverage (the number of times a base is read), which is useful for detecting rare variants and mosaic mutations. Whole Exome Sequencing (WES) sequences the protein-coding regions (exons) of all ~20,000 human genes. It is highly effective for identifying de novo mutations and can achieve a diagnostic yield of up to 50% in DEE cohorts. Whole Genome Sequencing (WGS) is the most comprehensive method that analyzes the entire genome, including non-coding regions. It excels at detecting complex structural variants, copy number variations (CNVs), and deep intronic mutations that WES or panels might miss. Hundreds of genes (>900) [7,14] now associated with DEE phenotypes. Identifying disease-causing genes and delineating their associated phenotypic spectra are essential for informing mechanism-based therapeutic strategies and enabling precision treatment across heterogeneous clinical conditions [144,147].

Most pathogenic variants for DEE arise de novo and disrupt fundamental neurobiological processes, including ion channel function (e.g., SCN1A, KCNQ2, CACNA1A), synaptic transmission and plasticity (e.g., STXBP1, SYNGAP1), cytoskeletal and membrane trafficking pathways, and chromatin regulation/epigenetic control. Exome data of DEE patients reveals de novo and inherited pathologic variants in epilepsy-associated genes [152].

In addition to monogenic causes, a smaller fraction of DEEs may result from autosomal recessive, X-linked, mosaic, or oligogenic inheritance, and structural variations such as copy number variants further expand the genetic etiology [146]. These genetic defects can perturb neuronal excitability, network development, and synaptic homeostasis, producing a spectrum of clinical manifestations that blur traditional syndrome boundaries and challenge genotype–phenotype correlations [15]. At the molecular level, the genetic landscape of DEEs reveals multiple pathogenic mechanisms beyond classical channelopathies. While ion current abnormalities underlie many cases by altering neuronal firing thresholds and excitability, synaptopathies and metabolic and neurodevelopmental pathway disruptions are also prominent [153]. Gene variants that affect neuronal progenitor proliferation, migration, and axon/dendrite development can produce malformations of cortical development, contributing both to epileptogenesis and intellectual disability. Genetic causes of DEE can be categorized based on their pathogenic mechanisms:

5.1. Ion Channelopathies:

These are among the most frequent genetic causes of DEEs and result from pathogenic variants in genes encoding voltage-gated sodium, potassium, calcium, or ligand-gated ion channels [7,13,14,141–144]. Disruption of ion conductance alters neuronal excitability, leading to early-onset seizures and epileptic network instability. Classic examples include *SCN1A* (Voltage-gated sodium channel α1 (Na_v1.1), Dravet syndrome), *SCN2A* (Voltage-gated sodium channel α2 (Na_v1.2)), *SCN3A* (Voltage-gated sodium channel α3), *KCNQ2* (Voltage-gated potassium channel (Kv7.2)), *KCNT1* (Potassium channel (Slack)), *CACNA1A/B/C/D/E* (Voltage-gated calcium channels), and *HCN1*

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(Hyperpolarization-activated cyclic nucleotide-gated channel**)**. Both gain- and loss-of-function mechanisms are observed, with important implications for treatment selection (e.g., sodium channel blockers vs avoidance).

5.2. Synaptopathy and Neurotransmission Disorders:

This category includes genes involved in synaptic vesicle release, receptor trafficking, scaffolding, postsynaptic signaling, and synaptic plasticity [7,13,14,141–144]. Defects impair communication between neurons, leading to abnormal circuit maturation and sustained epileptiform activity. These disorders often present profound developmental delays, hypotonia, and movement disorders in addition to epilepsy. Representative genes are *STXBP1* (Synaptic vesicle fusion / release), *SNAP25* (Presynaptic SNARE complex), *SYNGAP1* (Postsynaptic density scaffolding), *DNM1* (dynamin-1, clathrin-mediated endocytosis and other vesicular trafficking processes), *GRIN1* / *GRIN2A* / *GRIN2B* / *GRIN2D* (NMDA receptor subunits), *GABRA1* / *GABRB1* / *GABRB3* / *GABRG2* (GABA_A receptor subunits), *CNTNAP2* (Contactin-associated protein), and *SHANK3* (synapse formation and dendritic spine maturation).

5.3. Transport Genes:

Genes encoding membrane transporter components [7,13,14,141–144] constitute a major mechanistic class of DEEs, reflecting the exquisite dependence of the developing brain on tightly regulated ionic, neurotransmitter, and energy homeostasis. Transporter-related DEEs most commonly involve solute carrier (SLC) and ATP-binding cassette (ABC) families that regulate glucose, amino acids, neurotransmitters, and ions across neuronal and glial membranes. *SLC1A2* / *SLC6A1* / *SLC12A5* are neurotransmitter transporter genes. A paradigmatic example is *SLC2A1 (GLUT1)*, in which haploinsufficiency causes cerebral glucose transport deficiency leading to early-onset epilepsy and developmental impairment, often responsive to ketogenic therapy. Similarly, defects in *SLC6A1* (GABA transporter 1) disrupt inhibitory neurotransmission and are a frequent cause of epilepsy with developmental delay, while *SLC13A5* mutations impair citrate transport, linking intermediary metabolism to neuronal excitability. *ALG13* / *ST3GAL3* encodes glycosylation enzymes (affect synapse/neuronal development). Ion and metal transporters such as ATP1A3 (Na^+/K^+-ATPase $\alpha 3$) and *SLC12A5 (KCC2)* further highlight how disturbed electrochemical gradients and chloride homeostasis can directly precipitate epileptic encephalopathy phenotypes.

5.4. Metabolic and Mitochondrial Disorders:

Metabolic pathway genes [7,13,14,141–144] implicated in DEE predominantly converge on mitochondrial energy metabolism, amino acid and organic acid metabolism, and vitamin/cofactor pathways, underscoring the coupling between bioenergetics and neurodevelopment. Mutations in mitochondrial genes such as *POLG* (mitochondrial DNA polymerase subunit gamma), *TWNK* (twinkle mitochondrial DNA helicase), *NDUFS2*(NADH ubiquinone oxidoreductase core subunit S2, a subunit of mitochondrial complex I), *MT-ATP6* (mitochondrially encoded ATP synthase membrane subunit 6), and *SLC25A22* (mitochondrial glutamate transporter) lead to epileptic encephalopathies through impaired oxidative phosphorylation, redox imbalance, and excitotoxic vulnerability. In these DEEs, epilepsy arises secondary to energy failure, toxic metabolite accumulation, or impaired redox homeostasis, making neurons particularly vulnerable. Disorders of amino acid and neurotransmitter metabolism—including *ALDH7A1* (pyridoxine-dependent epilepsy), *PNPO* (Pyridoxamine 5''-Phosphate Oxidase), *SURF1* (a component of the mitochondrial translation regulation assembly intermediate of cytochrome c oxidase complex) and *GLDC* (Glycine Decarboxylase) demonstrate that subtle disruptions in metabolic flux can have profound effects on early neuronal circuit formation and seizure threshold, often with actionable treatment implications. Collectively, transport and metabolic DEEs illustrate a unifying principle: failures in substrate delivery, waste removal, or energy

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generation during critical developmental windows can transform seizures from symptoms into drivers of persistent encephalopathy.

5.5. Chromatin Remodeling and Epigenetic Regulation Disorders:

These genes encode proteins involved in DNA methylation, histone modification, transcriptional regulation, and chromatin architecture [7,13,14,141–144]. Disruption of epigenetic regulatory genes leads to widespread dysregulation of gene expression during critical developmental windows, affecting synapse formation and neuronal identity. Epilepsy is often part of a broader neurodevelopmental syndrome. Representative genes are *MECP2* (Chromatin regulator, Rett syndrome), *CDKL5* (Serine/threonine kinase, associated with early infantile), *CHD2* (Chromatin helicase DNA binding protein), *FOXG1* (Transcription factor, DEE phenotype with microcephaly), *ARX* (Homeobox transcription factor), KMT2A (encodes a DNA-binding protein that methylates histone H3), and *SETD1B* (encodes a lysine-specific methyltransferase that assists in transcriptional activation of genes by depositing H3K4 methyl marks).

5.6. Malformations of Cortical Development

Cerebral cortical development depends on the precisely timed activation and repression of tightly regulated genetic programs that govern neural progenitor proliferation and differentiation, neuronal specification and migration, and the assembly of functional neuronal circuits. Disruption of this coordinated developmental sequence compromises the formation of a properly functioning cortex. Accordingly, malformations of cortical development (MCDs) [28] arise from perturbations in these fundamental processes and are characterized by structural and functional abnormalities of the cerebral cortex. Pathogenic variants underlying MCDs frequently affect genes encoding chromatin modifiers, transcription factors, and RNA-binding proteins, underscoring the central role of epigenetic and transcriptional regulation in orchestrating neurogenesis and cortical patterning. Mutations in such genes cause neurodevelopmental disorders in DEE, including genes [28], disrupt neuronal proliferation (*ACTL6B, INPP4A, SMC1A, GEMIN5, HNRNPU*), differentiation (*CUX2, GNAO1, SP9*), migration (*DCX, TUBA1A*), and dendrito- or axonogenesis (*CYFIP2, RHOBTB2, DYNC1H1, SPTAN1, EEF1A2*).

5.7. Copy Number Variants (CNVs) and Structural Genomic Abnormalities:

Another class of DEE genes are not monogenic mutations, but contain copy number variants (CNV) [146,154,155] with submicroscopic deletions, duplications, or complex rearrangements can disrupt dosage-sensitive genes or regulatory regions critical for brain development. CNVs may act alone or modify the severity of monogenic DEEs. Representative loci are 15q13.3, 16p11.2, 2q24 (sodium channel cluster).

5.8. Genetic Heterogeneity in DEE:

DEEs are among the most genetically heterogeneous neurological disorders, reflecting disruption of multiple, convergent biological pathways essential for early brain development and network stability. Genetic heterogeneity in DEE encompasses multiple genes, inheritance patterns, variant types, functional classes, variable penetrance, and expressivity, all of which contribute to overlapping clinical phenotypes. This diversity underscores the importance of comprehensive molecular diagnostics, genotype-informed treatment strategies, and continued research to unravel convergent disease mechanisms. Genetic heterogeneity in DEE reflects the remarkable complexity of the disorder at the molecular level.

5.8.1. Locus Heterogeneity

Different genes (loci) can cause similar DEE phenotypes. It involves multiple genes, each of which can independently give rise to similar clinical manifestations. For example, pathogenic

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variants in *SCN1A, KCNQ2, STXBP1,* and *CDKL5*—genes with distinct biological roles—can all lead to early-onset seizures, developmental delay, and intellectual disability. DEE conditions like Infantile Spasms Syndrome (ISS) and Lennox-Gastaut Syndrome (LGS) are highly heterogeneous, resulting from variants in numerous different genes. This phenomenon, known as "locus heterogeneity," means that clinically similar DEE phenotypes may arise from entirely different molecular mechanisms.

5.8.2. Allelic Heterogeneity

Allelic heterogeneity and functional variation contribute to heterogeneous genetic and phenotypic complexity in DEE. Different pathogenic variants within the same gene can produce variable clinical outcomes. Truncating, missense, or splice-site mutations can produce markedly different clinical outcomes even when affecting the same gene. The specific type of mutation within a single gene significantly impacts the clinical phenotype, leading to "pleiotropy" of the clinical presentations. For instance, truncating variants in *KCNQ2* often result in severe neonatal DEE, whereas certain missense variants may present as milder, self-limited neonatal epilepsy. The gain-of-function (GOF) vs. loss-of-function (LOF) variants in genes like *SCN1A, SCN2A*, and *SCN8A*, result in different time of onset and clinical severity. GOF mutations often result in earlier (neonatal) onset and severe encephalopathy, while LOF mutations may lead to later-onset infantile epilepsy or Dravet Syndrome. This allelic heterogeneity underscores the importance of detailed variant-level interpretation in both research and clinical settings.

5.8.3. Phenotypic Pleiotropy

The same genetic variant can result in diverse clinical manifestations. *SCN2A* variants exemplify this, causing either benign neonatal epilepsy or severe DEE depending on variant type and functional impact, making clinical prognostication challenging.

5.8.4. Diverse Molecular Classes

DEE genes span multiple functional classes, including ion channels, synaptic machinery, transcriptional regulators, and metabolic enzymes. Despite this functional diversity, there is often convergence on common pathophysiological pathways, such as impaired neuronal excitability, disrupted synaptic transmission, or abnormal neurodevelopment. This convergence explains why phenotypically similar DEEs can arise from mutations in genes with vastly different primary functions.

5.8.5. Diverse Inheritance Patterns

DEE also exhibits diverse inheritance patterns. While de novo mutations are the most common cause of sporadic DEE, autosomal recessive forms are increasingly recognized, particularly in consanguineous populations. Additionally, X-linked forms affect males and females differently, as exemplified by CDKL5-related DEE. These variable inheritance patterns complicate genetic counseling and necessitate careful family history assessment alongside molecular testing. DEE involved mitochondrial genes follow maternal inheritance patterns for mitochondrial genome.

5.8.6. Implications for Diagnosis and Therapy:

This multifaceted genetic heterogeneity [156] of DEE makes molecular diagnosis gene-based therapy challenging yet crucial. There is a critical need for comprehensive molecular diagnostics, such as next-generation sequencing (NGS) panels or whole-exome/genome sequencing, which are to identify causative variants accurately. Gene-specific therapies are emerging, such as antisense oligonucleotides Zorevunersen for *SCN1A*-related DEE [157] or precision pharmacotherapy [158,159] for LOF or GOF variants of *KCNQ2*, highlighting the need for accurate genetic characterization.

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Variant interpretation complexity of DEE arises from the substantial number of rare variants, variable expressivity, and incomplete penetrance. Functional studies or *in silico* modeling often aid in establishing pathogenicity. Moreover, it highlights the potential for genotype-informed treatment strategies, as specific variants or genes may predict response to particular anti-seizure medications or emerging gene-targeted therapies.

Understanding the broad spectrum of genetic causes and their shared mechanistic pathways is essential for research aimed at unraveling convergent disease mechanisms, which may ultimately guide the development of novel therapeutic interventions across genetically heterogeneous forms of DEE.

6. Non-Genetic Etiology for Developmental and Epileptic Encephalopathy (DEE)

While a substantial proportion of DEE cases are attributed to identifiable genetic mutations, a significant subset arises from non-genetic etiologies or have unknown causes even after extensive genomic testing. In cohort studies of infants with infantile spasm (a type of DEE) it was found that a significant proportion of cases result from non-genetic causes. Specifically, approximately 40–60% of cases are attributed to structural (genetic or acquired), metabolic, or infectious etiologies [15,48,160]. This highlights the limits of genetics alone in explaining these disorders.

Congenital or acquired structural brain abnormalities, such as cortical malformations due to prenatal insults, perinatal hypoxic-ischemic injury, vascular lesions, or trauma, can disrupt neuronal networks in ways that predispose to both seizures and developmental delay independent of monogenic causes. Similarly, metabolic derangements (e.g., inborn errors of metabolism or severe systemic metabolic stress) can alter neuronal excitability and energy supply, resulting in encephalopathy with epileptic manifestations. Infectious and inflammatory processes**,** including congenital infections (e.g., cytomegalovirus, toxoplasmosis, or rubella) and post-infectious immune-mediated encephalitides, also contribute to DEE phenotypes by causing direct brain injury and secondary epileptogenesis. These non-genetic triggers [15] may act alone or synergistically with genetic susceptibilities to produce the severe, treatment-resistant seizures and developmental impairments characteristic of DEEs.

Beyond gross structural or acquired insults, environmental and toxic exposures [161–163] during critical periods of brain development (*in utero* or early infancy) can contribute to epileptic encephalopathy by interfering with neurogenesis, synaptogenesis, and network maturation. Although direct evidence linking specific environmental neurotoxicants to classical DEE phenotypes is limited, broader developmental neurotoxicity literature implicates agents such as heavy metals, organic solvents, and other developmental toxicants in adverse neurodevelopmental outcomes, theoretically lowering seizure thresholds or contributing to epileptogenesis in vulnerable brains. Epidemiological and mechanistic studies of developmental toxicity — including those establishing lead, methylmercury, and other chemicals as harmful to the developing brain — underscore how non-genetic factors can alter neuronal circuitry and predispose to severe neurodevelopmental disorders that phenotypically overlap with DEEs.

Growing evidence implicates neuroinflammatory [164–166] and neurodegenerative [167–169] processes in modifying disease progression in genetically defined DEEs, suggesting an interplay between early developmental disruption and later network instability [167]. Neuroinflammatory and neurodegenerative processes are increasingly recognized as central, bidirectional contributors to the pathophysiology of DEE, rather than merely downstream consequences of recurrent seizures. In the developing brain, seizures robustly activate innate immune signaling pathways, leading to sustained microglial [165,166] and astrocytic [170,171] activation. These glial cells release proinflammatory cytokines and chemokines—such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and high-mobility group box 1 (HMGB1) that directly modulate neuronal excitability by altering ion channel function, neurotransmitter receptor trafficking, and synaptic homeostasis. Concurrent disruption of the blood–brain barrier facilitates peripheral immune cell infiltration and amplifies local inflammation. In the immature brain, where synaptogenesis, circuit refinement, and activity-

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dependent plasticity are tightly regulated, chronic neuroinflammation interferes with critical developmental programs, resulting in maladaptive network wiring that both promotes epileptogenesis and impairs cognitive and behavioral outcomes characteristic of DEE.

In DEE, genetic, neurodegeneration, and neuroinflammation are increasingly recognized as the result of a "pathogenic triad" or convergence of factors [167–169]. Neurodegenerative processes in DEE often emerge from the convergence of intrinsic genetic vulnerabilities and inflammation-driven excitotoxicity. Many DEE-associated gene variants affect proteins essential for synaptic stability, mitochondrial function, proteostasis, or axonal transport, rendering neurons particularly susceptible to metabolic stress. Persistent seizures and inflammatory signaling exacerbate mitochondrial dysfunction, oxidative stress, and calcium dysregulation, ultimately triggering apoptotic or necrotic neuronal loss. Importantly, neurodegeneration in DEE is not always uniform or progressive in a classical sense; instead, it may manifest as regionally selective neuronal loss, dendritic simplification, impaired myelination, or failure of normal neuronal maturation. These degenerative-like changes further destabilize neural circuits, reinforcing seizure burden and accelerating developmental regression or stagnation.

Critically, neuroinflammation and neurodegeneration form a “self-perpetuating pathogenic loop” or "vicious cycle" [167–169] in DEE where initial inflammatory responses drive neuronal damage, which in turn triggers further inflammation. Inflammatory mediators lower seizure threshold and impair synaptic plasticity, while ongoing seizures and neuronal injury continuously reactivate immune pathways. This vicious cycle helps explain why early-onset, uncontrolled seizures are strongly associated with worse developmental trajectories and why seizure suppression alone is often insufficient to halt cognitive decline. Emerging evidence from both human studies and animal models suggests that targeting neuroinflammatory pathways—through modulation of microglial activation, cytokine signaling, or mitochondrial resilience—may offer disease-modifying strategies in DEE. Conceptually, this framework positions DEE not only as a disorder of aberrant excitability but also as a chronic neuroimmune and neurodegenerative condition of the developing brain.

These insights have important clinical implications: genetic diagnosis informs precision medicine approaches, enables targeted therapies where available, and supports genetic counseling and prenatal decision-making for affected families [143].

7. Seizure-Driven Disruption of Neurodevelopment

DEEs are primarily defined by high rates of drug-resistant (refractory) epilepsy that is unresponsive to standard antiseizure medications (ASMs). Among all epilepsy patients, about ~1/3 are refractory. However, the rate for ILEA defined drug-resistant epilepsy (DRE) [172] was found higher among DEE patients, about 77.7% [173]. Most DEE patients continue to have frequent, uncontrollable, seizures.

Early-life seizures can significantly disrupt neurodevelopment [174–176] by perturbing activity-dependent processes that are essential for synaptic formation [177] for brain connectivity, myelination [178], normal brain maturation neurotransmitter systems, and cognitive trajectory. The most severe impacts typically occur when seizures are frequent, prolonged, or occur during critical time periods [179]. During early life, neuronal activity is not merely permissive, but is instructive for neurodevelopment, guiding neurogenesis, neuronal migration, synaptogenesis, circuit refinement, and myelination.

Activity-dependent plasticity [180–184] is a fundamental mechanism by which neuronal activity shapes synaptic strength, circuit architecture, and gene expression during brain development and throughout life. In the developing brain, patterned spontaneous and sensory-driven activity instructs synapse formation [177], elimination, and stabilization, thereby refining neural circuits and establishing excitatory–inhibitory balance. At the molecular level, activity-dependent plasticity is mediated by calcium influx through NMDA receptors and voltage-gated calcium channels, which activate intracellular signaling cascades involving CaMKII [185–187], ERK/MAPK [188,189], BDNF [190,191], and CREB [192,193] signaling cascades. These pathways couple synaptic activity to

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transcriptional and translational programs that regulate receptor trafficking, dendritic spine remodeling, and long-term changes in synaptic efficacy, exemplified by long-term potentiation (LTP) [194–196] and long-term depression (LTD) [197]. Pathological hypersynchronous activity associated with seizures can therefore derail these tightly regulated programs, leading to persistent alterations in brain structure and function.

In DEE, activity-dependent plasticity is frequently distorted [29,198] by early-onset seizures that "drown out" normal neuronal activities that need to take place in critical developmental time periods for normal brain formation [29,179,199]. Rather than supporting adaptive circuit refinement for normal brain development, excessive or aberrant neuronal activity can drive maladaptive plasticity, reinforcing hyperexcitable networks and impairing normal developmental trajectories. Recurrent seizures during critical periods [200,201] alter synaptic scaling, disrupt inhibitory interneuron maturation, and modify homeostatic plasticity mechanisms, leading to persistent network instability and cognitive impairment. The maladaptive plasticity from early-life seizures (ELS) [202–204] rewires brain networks, significantly increasing long-term susceptibility to further epilepsy and cognitive deficits. The century-old observation of "seizures beget more seizures" [205–208] is even more detrimental in DEE with early-life seizures occurring in critical time windows of neurodevelopment.

Moreover, many DEE-associated genes encode proteins directly involved in synaptic transmission, ion channel function, or activity-regulated transcription, linking genetic vulnerability to activity-driven circuit dysfunction. Thus, pathological engagement of activity-dependent plasticity represents a central mechanism by which seizures and underlying molecular defects converge to exacerbate epilepsy severity and neurodevelopmental impairment in DEE.

8. Bidirectional Relationship of DEE and Primary Mitochondrial Disease (PMD)

Primary Mitochondrial Diseases (PMD) [35,209,210] caused by mutations in mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) encoding mitochondrial components, frequently manifest as DEE because the brain's high energy demands cannot be met. DEE and PMD share a bi-directional relationship where each condition can function as both a cause and a consequence of the other, often forming a destructive "vicious cycle" of neurodegeneration. Both DEE and PMD are marked by high-energy demand in the central nervous system, making them susceptible to the same metabolic and electrical disruptions. They are increasingly recognized as biologically intertwined disorders, linked through shared vulnerabilities in neuronal energy metabolism, redox homeostasis, and activity-dependent network maturation.

8.1. PMD as a Cause for DEE - Epilepsy

Epilepsy represents the most frequent manifestation of central nervous system involvement in PMD [211–214], affecting 35%-60% of patients diagnosed with mitochondrial diseases[208]. Common PMDs, such as mitochondrial myopathy encephalopathy, lactic acidosis and stroke-like episodes (MELAS) [215–217], myoclonus epilepsy and ragged-red fibers (MERRF) [218–220], and polymerase gamma (POLG) [221–223] all present seizures with clinical symptoms. MELAS have seizures as one of the disease's most common manifestations[218-221], with a lifetime prevalence that typically ranges from 71% to 96% of patients. The prevalence of MELAS patients that experience at least one seizure has even been found at 100% in some cohorts. In MERRF, seizures are a defining clinical feature, with a prevalence significantly higher than in general mitochondrial disease cohorts. In patients harboring m.8344A>G MERRF mutation, the prevalence of epilepsy is approximately 92.3% [224], whereas the epilepsy prevalence is 34.9% for patients with the most common m.3243A>G variant [224]. For patients clinically diagnosed with the full "classic" MERRF phenotype, the prevalence of myoclonus and generalized epilepsy often reaches 100% in specific study cohorts. In POLG-related mitochondrial disorders [225–228], the prevalence of seizures varies significantly based on the age of disease onset. Approximately 71% of patients with POLG mutations develop seizures during their lifetime. For POLG patients with early-Onset (<12 years), seizure prevalence is highest in this group, affecting approximately 84% to 97% of patients. Approximately 71% of Juvenile/Adult-Onset (12–40

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years) POLG patients in this age bracket experience seizures. Seizures are less common as a primary feature in older adults with late onset (>40 years), though they can still occur.

8.2. Mitochondrial Dysfunction Lower Seizure Threshold

Mitochondrial dysfunctions can lower the seizure threshold by directly destabilizing the energetic, redox, ionic, and signaling homeostasis that normally restrains neuronal excitability. Because neurons operate close to their bioenergetic and electrophysiological limits, even modest mitochondrial impairment can shift networks toward hypersynchrony and seizure generation.

8.2.1. Lower Seizure Threshold via Bioenergetic Crisis, Ion Channels, and Cell Death

Mitochondria are the primary source of neuronal ATP required to maintain membrane potential via Na^+/K^+-ATPase and Ca^{2+} pumps. When oxidative phosphorylation is impaired, ATP levels fall, leading to incomplete repolarization after action potentials. This results in membrane depolarization, increased spontaneous firing, and enhanced network excitability. ATP depletion also compromises inhibitory interneurons, which are especially energy-demanding, tipping the excitation–inhibition balance toward excitation. Altered mitochondrial redox states lead to changes in mitochondrial membrane potentials, resulting in swelling of the intermembrane space and transports across the mitochondrial membranes of $Ca^{2+,}$ H^+, ATP/ADP, and releasing cytochrome c, a signal for cell death [229–231]. Bioenergetic failure can lead to metabolic stress then into electrical instability.

8.2.2. Lower Seizure Threshold via Calcium Dysregulation and Excitotoxicity

Mitochondria is a key regulator for intracellular Ca^{2+} homeostasis during synaptic activity. Dysfunctional mitochondria have reduced Ca^{2+} uptake capacity, causing cytosolic Ca^{2+} accumulation. Elevated Ca^{2+} enhances glutamate release, activates NMDA receptors, and promotes sustained depolarization. Excess Ca^{2+} also triggers mitochondrial permeability transition, further impairing ATP production and reinforcing hyperexcitability. Mitochondrial dysfunctions leading to impaired mitochondrial Ca^{2+} handling which amplifies excitatory neurotransmission.

8.2.3. Lower Seizure Threshold via Oxidative Stress and Cell death

Mitochondrial electron transport chain (ETC) not only transfers electrons from NADH to ubiquinone for oxidative phosphorylation (OxPhos), but is also a major source of reactive oxygen species (ROS) [232–236]. Impaired ETC cannot properly capture electrons resulting in increased ROS, mtDNA mutations [237] and cellular damage. ROS can signal cell death (necrosis, apoptosis, pyroptosis, ferroptosis) [238,239]. Oxidative damage to mitochondrial DNA and respiratory chain complexes further exacerbates bioenergetic failure, creating a feed-forward loop between oxidative stress and seizures.

8.2.4. Lower Seizure Threshold via Oxidative Stress and Redox-Sensitive Ion Channels

ROS can modify redox-sensitive ion channels (e.g., voltage-gated Na^+ and K^+ channels), lowering firing thresholds and prolonging action potentials. ROS modifies redox-sensitive ion channels [240] primarily through oxidative post-translational modifications (PTMs) of cysteine residues. Transient receptor potential melastatin 2 (TRPM2) [241–245] is widely cited as a direct sensor of oxidative stress that can modulate Ca^{2+} influx, in turns, alter action potentials [246]. ROS can modify voltage-gated K^+ channels [247–249] by oxidizing thiol groups in the pore-forming α subunits or regulatory β subunits. in turns, alter action potentials [246]. Thus, mitochondrial dysfunction increases ROS leading to persistent neuronal hyperexcitability.

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8.2.5. Lower Seizure Threshold via Impaired Inhibitory Neurotransmission

GABAergic interneurons are highly dependent on mitochondrial metabolism. GABAergic interneurons [250–252], particularly fast-spiking parvalbumin-expressing (PV+) cells, are among the most metabolically demanding cells in the brain due to their continuous high-frequency firing and rapid synaptic transmission. The high mitochondrial content in PV+ interneurons is necessary to provide the precise ATP supply required for high-speed neuronal signaling and the generation of gamma oscillations (30–80 Hz), which are essential for cognitive processing. Mitochondrial dysfunction preferentially impairs these cells, reducing GABA synthesis and release. In parallel, ATP-dependent GABA reuptake and vesicle loading become inefficient. This has a net effect of both a weakened inhibitory tone and a lower threshold for synchronized firing.

8.2.6. Lower Seizure Threshold via Altered Mitochondrial Signaling and Network Plasticity

Mitochondria regulate apoptosis, inflammation, and activity-dependent gene expression. Chronic mitochondrial stress activates inflammatory signaling and maladaptive plasticity that remodels synapses toward hyperexcitable states. Over time, this can lower seizure threshold at the network level, explaining why mitochondrial dysfunction is strongly associated with refractory epilepsy and DEE. Mitochondria influence not only acute excitability but long-term epileptogenesis.

8.3. PMD as a Cause for DEE - Neurodevelopment Deficits

Mitochondria functions as central regulators of neurodevelopment, governing ATP production, calcium buffering, reactive oxygen species signaling, apoptosis, and epigenetic programming during critical periods of brain maturation [253,254]. Consequently, primary defects in mitochondrial DNA or nuclear-encoded mitochondrial genes frequently manifest with early-onset seizures and developmental impairment, placing primary mitochondrial diseases (PMDs) among the most common metabolic etiologies of developmental and epileptic encephalopathy (DEE) [7,13,14,141–144]. Pathogenic variants affecting oxidative phosphorylation, mitochondrial dynamics, or mitochondrial protein translation disrupt neuronal excitability thresholds and synaptic development. These perturbations predispose immature neural circuits to epileptogenesis while simultaneously impairing cognitive and motor trajectories in mitochondrial encephalopathy [255–258].

8.4. DEE as a Cause of Mitochondrial Dysfunction

One class of DEE is caused by mitochondrial mutations or nuclear mutations affecting mitochondrial genes (as in 4.4). Additionally, other types of DEE can precipitate secondary mitochondrial dysfunction, creating a self-reinforcing pathological feedback loop that accelerates disease progression.

This bidirectional interaction is particularly evident in genetic DEEs caused by pathogenic variants in ion channels, synaptic proteins, or chromatin regulators. In these disorders, the primary genetic defect disrupts neuronal excitability or gene regulation, leading to early-onset seizures that secondarily drive mitochondrial dysfunction. Rather than serving as the initiating insult, mitochondrial abnormalities emerge downstream as disease-amplifying factors that intensify network hyperexcitability and neurodevelopmental impairment. Recognizing mitochondrial dysfunction as a consequence—and propagator—of epileptic activity in DEE reframes it as a critical therapeutic target, with the potential to interrupt this vicious cycle and mitigate both epileptic severity and developmental decline.

Importantly, the convergence of DEE and PMD reflects shared pathogenic pathways rather than discrete disease categories. Mitochondrial dysfunction acts as both a primary driver of epileptic encephalopathy and a secondary modifier that worsens seizure burden and developmental outcomes. This conceptual framework has therapeutic implications, supporting the integration of metabolic evaluation in DEE and highlighting mitochondria-targeted interventions—such as

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ketogenic therapies, redox modulation, and enhancement of mitochondrial biogenesis—as rational adjunctive strategies in selected patients. Understanding DEE and PMD as components of a dynamic, bidirectional disease continuum provides a unifying model for explaining clinical heterogeneity and treatment refractoriness in early life epilepsies.

9. Convergent of Mitochondrial Dysfunction in DEE

Although DEEs exhibit genetic and phenotypic heterogeneity, their diverse etiologies converge on mitochondrial dysfunction as a shared pathogenic mechanism. Some DEEs are caused by mitochondrial mutations. Other types of DEEs can precipitate secondary mitochondrial dysfunction, creating a self-reinforcing pathological feedback loop that accelerates disease progression. Pathogenic variants affecting ion channels, synaptic proteins, transcriptional and epigenetic regulators, and metabolic pathways produce wide variability in clinical presentation, yet commonly result in impaired OxPhos, reduced ATP availability, dysregulated calcium handling, and oxidative stress in vulnerable neuronal populations.

9.1. Mitochondrial Dysfunctions Caused by Mitochondrial Mutations in DEE

A subset of DEEs as PMDs are caused by mitochondrial mutations or nuclear mutations affecting mitochondrial genes (as in 4.4).

9.2. Mitochondrial Dysfunctions Caused by Seizures in DEE

Seizures impose one of the most extreme physiological stressors on neurons, acutely challenging cellular bioenergetic capacity and homeostatic control. Seizures can cause mitochondrial injury, initiating a cascade of metabolic, structural, and transcriptional abnormalities that persist beyond the ictal period. This seizure-induced mitochondrial dysfunction contributes to epileptogenesis, disease progression, and neurodevelopmental impairment, particularly in DEE. Seizure-driven hyperexcitability imposes extreme bioenergetic demands that damage mitochondrial integrity, while defects in gene regulation, mTOR signaling, proteostasis, and mitophagy further compromise mitochondrial biogenesis and quality control. Mitochondrial dysfunction, in turn, disrupts neurodevelopmental processes, synaptic plasticity, and excitatory–inhibitory balance, reinforcing a vicious cycle in which energetic failure lowers seizure thresholds and recurrent seizures exacerbate metabolic stress. This convergence on mitochondrial pathology provides a unifying framework linking genetic diversity to shared clinical severity in DEE and highlights mitochondrial pathways as broadly relevant targets for disease-modifying therapies.

9.2.1. Acute Bioenergetic Failure

Seizures cause acute bioenergetic failure and metabolic collapse through a rapid mismatch between massive energy demand and the brain's finite metabolic supply [259–264]. During seizures, sustained neuronal depolarization and hypersynchronous firing dramatically increase ATP demand to support ion gradient restoration, synaptic vesicle cycling, and neurotransmitter clearance. Mitochondria initially respond by upregulating oxidative phosphorylation; however, prolonged or recurrent seizures rapidly exceed this compensatory capacity, resulting in ATP depletion and phosphocreatine exhaustion. Energy failure compromises Na^+/K^+-ATPase and Ca^{2+}-ATPase activity, perpetuating membrane depolarization and excitability. In severe cases, ATP synthase reverses activity to maintain mitochondrial membrane potential, further exacerbating cytosolic energy depletion. These events establish a feedforward mechanism in which metabolic failure amplifies neuronal hyperexcitability rather than terminating it.

9.2.2. Metabolic Collapse, Lactate Accumulation, and Metabolic Acidosis:

Heightened neuronal activity shifts the brain toward aerobic glycolysis, resulting in a surge of lactate and extracellular acidosis [265–268]. While this can function as a natural anticonvulsant to stop

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a seizure, it also reflects a state of severe metabolic stress. Proton magnetic resonance spectroscopy (^{1}H-MRS) found the most consistent finding after seizures is a significant reduction in N-acetylaspartate (NAA) levels in patients with temporal lobe epilepsy (TLE) [269–271] and in rodent models of status epilepticus [272,273]. NAA levels (often measured as ratios such as NAA/Cr or NAA/Cho) typically decrease in the ipsilateral hippocampus or the specific epileptogenic focus immediately following a seizure. NAA is a neuronal mitochondrial marker. Reduction in NAA is a primary marker for neuronal loss or neuronal mitochondrial dysfunction.

9.2.3. Calcium Overload as a Central Mitochondrial Insult

Prolonged seizures impair mitochondrial functions by Ca^{2+} overload [264,274,275]. by causing membrane depolarization and opening the mitochondrial permeability transition pore (mPTP) [276] and mitochondrial Ca^{2+} uniporter (MCU) [277]. This disruption leads to a failure in calcium buffering and increased production of reactive oxygen species (ROS), further damaging respiratory enzymes. Excessive calcium influx [278] is a defining feature of seizure activity, mediated by NMDA receptors [279–281], calcium-permeable AMPA receptors [282,283], and voltage-gated calcium channels [264,274,275]. Mitochondria function as major calcium buffers during physiological neuronal activity; however, during seizures, sustained calcium uptake overwhelms mitochondrial handling capacity. Elevated intramitochondrial calcium disrupts electron transport chain function, depolarizes the inner mitochondrial membrane, and promotes opening of the mitochondrial permeability transition pore (mPTP). Even transient mPTP opening can cause lasting impairment of oxidative phosphorylation and increase susceptibility to subsequent metabolic stress.

9.2.4. Oxidative Stress and Mitochondrial Genome Instability

Seizures trigger a "vicious cycle" where excessive neuronal firing generates reactive oxygen species (ROS), which directly cause mitochondrial DNA (mtDNA) damage [284–287], thus mitochondrial genome instability. This mitochondrial dysfunction, in turn, increases neuronal hyperexcitability, predisposing the brain to further seizures. Seizure-driven hypermetabolism markedly increases the production of reactive oxygen and nitrogen species due to electron leakage from the respiratory chain. Mitochondrial DNA (mtDNA), which lacks protective histones and is in close proximity to the electron transport chain, is particularly vulnerable to oxidative damage. Recurrent seizures are associated with mtDNA mutations, deletions, and reduced transcription of mitochondrially encoded respiratory chain subunits, leading to progressive impairment of mitochondrial efficiency. Human epileptic brain tissue exhibits elevated markers of lipid peroxidation, protein oxidation, and oxidized mtDNA, and these changes can persist long after seizure cessation. Such findings support the concept that seizures leave a durable molecular imprint on mitochondria, contributing to chronic metabolic vulnerability.

9.2.5. Disruption of Mitochondrial Dynamics and Quality Control

Beyond metabolic impairment, seizures profoundly disrupt mitochondrial integrity, dynamic turnover, and mitochondrial quality control [288–290]. Mitochondrial function highly depends on tightly controlled fusion and fission dynamics [291]. Seizures trigger the activation and upregulation of mitochondrial fission machinery [292,293], specifically Dynamin-Related Protein 1 (DRP1) [294]. This excessive fission leads to mitochondrial fragmentation, while impaired fusion limits functional complementation between damaged and healthy mitochondria. Concurrently, seizures interfere with mitophagy pathways, resulting in the accumulation of dysfunctional mitochondria within neurons. Altered axonal and synaptic mitochondrial trafficking further compromises local energy supply at sites of high demand. These defects are especially consequential in the developing brain, where precise mitochondrial positioning and turnover are essential for synaptogenesis, circuit refinement, and activity-dependent plasticity. Seizure-induced disturbances in mitochondrial dynamics therefore

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provide a mechanistic link between epileptic activity and long-term neurodevelopmental impairment.

9.2.6. Implications of Seizures-Induced Mitochondrial Dysfunction on Neurodevelopment

The consequences of seizure-induced mitochondrial dysfunction extend beyond energy failure to profoundly influence neuronal development and circuit maturation. Impaired mitochondrial function disrupts activity-dependent processes such as synaptic pruning, dendritic growth, and axonal refinement, all of which are essential for normal neurodevelopmental plasticity. Chronic bioenergetic insufficiency and oxidative stress interfere with intracellular signaling pathways that link neuronal activity to gene expression, thereby blunting adaptive responses to experience. As a result, developmental trajectories are progressively derailed, manifesting clinically as developmental stagnation or regression that often parallels worsening seizure burden in DEE.

9.3. Mitochondrial Dysfunctions Caused by Ion Channelopathies in DEE

Pathogenic variants in ion channel genes, including voltage-gated sodium (SCN1A), potassium (KCNQ2/3), and calcium channels (CACNA1A), are major contributors to hyperexcitability in developmental and epileptic encephalopathies (DEE). These channelopathies disrupt neuronal membrane potential regulation, leading to recurrent or prolonged action potentials and abnormal firing patterns. Excessive neuronal firing imposes profound bioenergetic demands. Restoration of ionic gradients after action potentials relies predominantly on ATP-dependent pumps, such as the Na^+/K^+-ATPase and plasma membrane Ca^{2+}-ATPases. In parallel, mitochondria function as cytosolic calcium buffers, sequestering Ca^{2+} to maintain neuronal homeostasis. Channelopathy-induced sodium and calcium influx drives mitochondrial Ca^{2+} overload, depolarization of the inner mitochondrial membrane, and opening of the mitochondrial permeability transition pore (mPTP), collectively resulting in oxidative stress, impaired ATP production, and mitochondrial structural and functional perturbations. In experimental models of Dravet Syndrome, *SCN1A* exhibit mitochondrial dysfunction in heart and brain mutants, mitochondrial calcium overload mutants and increased oxidative stress mutants, resulting in elevated risk of Sudden Unexpected Death in Epilepsy (SUDEP) [295,296]. KCNQ2/3-deficient neurons [297,298] display reduced mitochondrial membrane potential under high-frequency firing.

9.4. Mitochondrial Dysfunctions Caused by Synaptopic and Neurotransmission Abnormalities in DEE

In DEE, mutations in genes primarily responsible for synaptic transmission (such as *STXBP1, SYNGAP1, DNM1, etc.*) can have overlap symptoms such as mitochondrial dysfunction. here are overlapping features between SYNGAP1 Syndrome [299] and mitochondrial disorders, such as intractable epilepsy, ASD, excessive fatigue, and altered biochemical markers [300,301]. De novo *STXBP1* mutation is associated with mitochondrial complex I [302] and mitochondrial complex IV deficiency [303]. Studies of *SHANK3* [304–306] identified that mitochondrial dysfunction as underlying mechanism for autism-associated phenotypes. While molecular mechanisms are under investigation, possible reasons for this mitochondrial dysfunction could be that neurons are highly energy-dependent, disruptions in the "handshake" between synaptic activity and mitochondrial supply create a toxic feedback loop. Normally, synaptic activity signals mitochondria to increase ATP production. Mutations in synaptic genes (like *STXBP1*) disrupt the docking and fusion of vesicles, causing irregular signaling. This prevents mitochondria from receiving the "cue" to ramp up energy, leading to a localized energy crisis.

9.5. Mitochondrial Dysfunctions Caused by Transport Genes in DEE

DEE mutations in transport genes disrupt the delicate metabolic and ionic balance of neurons, often leading to secondary mitochondrial dysfunction. While these genes primarily encode transporters on the cell surface, their failure triggers downstream effects—such as energy depletion,

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calcium overload, and oxidative stress—that directly impair mitochondrial health. *SLC2A1* encodes the *GLUT1* glucose transporter, which mediates glucose entry across the blood-brain barrier and into neurons. GLUT1 deficiency causing mitochondrial dysfunction [307]. GLUT1 deficiency syndrome (Glut1DS) [308–310] presents a broad clinical spectrum that frequently overlaps with other metabolic and mitochondrial disorders due to shared mechanisms of cerebral energy failure. *SLC6A1* encodes GAT-1, the main GABA (γ-aminobutyric acid) transporter in neurons. Loss-of-function variants in *SLC6A1* lead to reduced GABA reuptake, resulting in altered inhibitory neurotransmission, cortical hyperexcitability and lower seizure thresholds, which can indirectly result in mitochondrial injury and dysfunction (as in 9.2).

9.6. Mitochondrial Dysfunctions Caused by Regulatory Genes in DEE

In DEE, several specific genes involved in chromatin remodeling, transcriptional, and epigenetic regulation have been linked to mitochondrial dysfunction. These genes act as "master switches" that, when mutated, disrupt the energy-producing machinery of the neuron. *CHD2* (Chromodomain Helicase DNA-binding protein 2) [311] is one of the most frequently mutated genes in DEE. CHD2 is an ATP-dependent chromatin remodeler crucial for neurodevelopment. Its loss (haploinsufficiency) is a primary cause of CHD2-related neurodevelopmental disorders, leading to refractory seizures and impaired mitochondrial gene expression, which starves neurons of necessary ATP. *CDKL5* gene (Cyclin-Dependent Kinase-Like 5) [312,313] provides instructions for making a protein that acts as an essential regulator for brain development and maintenance. It is most active in the brain's forebrain neurons, particularly within the cerebral cortex and hippocampus. CDKL5 is a serine/threonine kinase highly enriched in neurons and is tightly coupled to activity-dependent synaptic signaling. Loss of CDKL5 impairs phosphorylation of key synaptic and cytoskeletal substrates CDKL5 shuttles between the cell's nucleus and cytoplasm to perform different tasks. In the nucleus, it is involved in pre-mRNA splicing and gene expression. In the cytoplasm, it interacts with the microtubule network to stabilize the structure of developing brain cells. In induced pluripotent stem cells (iPSC), derived from *CDKL5* patients [313,314] and *Cdkl5* mice [315,316], it had mitochondrial dysfunction. Methyl-CpG–binding protein 2 (*MeCP2*) is associated with Rett Syndrome [317,318]. iPSC derived from Rett Syndrome patients with *MeCP2* mutation also showed mitochondrial dysfunction [314]. *SETD1B* is a histone H3K4 methyltransferase regulating arrays of gene transcriptions. Mitochondrial structure and function depend on ~1,200 nuclear-encoded mitochondrial genes (NEMGs**)**. SETD1B-mediated H3K4me3 is critical for their transcription. SETD1B [319,320] is a key mediator of the metabolic shift and mitochondrial stress.

10. Mitochondria as Central Epigenetic Regulators of Neurodevelopmental Programming in DEE and PMD

Mitochondria function as central epigenetic regulators during neurodevelopment by coupling cellular metabolic state to chromatin architecture and gene expression programs that govern neural progenitor proliferation, differentiation, and maturation. Beyond ATP production, mitochondrial ETC and TCA cycle generate key metabolic intermediates [47,321–326] —including acetyl-CoA, α-ketoglutarate, succinate, fumarate, and NAD^+—that directly serve as substrates for acetylation and histone methylation, or cofactors for chromatin-modifying enzymes which can regulate epigenetic programming. Acetyl-CoA availability modulates histone acetyltransferase activity, thereby influencing chromatin accessibility and transcription of neurodevelopmental genes, whereas α-ketoglutarate supports the activity of TET DNA demethylases and Jumonji C-domain histone demethylases that are essential for dynamic DNA and histone demethylation during neuronal lineage specification. In contrast, accumulation of succinate and fumarate, as occurs in mitochondrial dysfunction, inhibits these dioxygenases, promoting a hypermethylated chromatin state that can lock neural cells into maladaptive developmental trajectories.

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Mitochondria serve as signaling hubs that regulate nuclear gene expression through metabolite-dependent epigenetic mechanisms [327–330]. Seizure-induced mitochondrial dysfunction alters levels of acetyl-CoA, NAD^+/NADH, and tricarboxylic acid cycle intermediates, thereby modulating histone acetylation, DNA methylation, and chromatin accessibility. These changes reprogram transcriptional networks governing synaptic function, ion channel expression, inflammatory signaling, and neurodevelopmental pathways. Such mitochondria-mediated epigenetic remodeling provides a plausible mechanism by which transient seizure activity produces long-lasting changes in neuronal identity and circuit behavior, contributing to epileptogenesis and developmental regression in DEE.

Mitochondrial redox signaling further integrates epigenetic control with neurodevelopmental timing [331]. Reactive oxygen species (ROS), produced at physiological levels during oxidative phosphorylation, act as signaling molecules that influence redox-sensitive transcription factors and epigenetic enzymes. Excessive or chronic ROS, however, can alter DNA methylation patterns, induce oxidative DNA damage, and modify histones, thereby disrupting gene regulatory networks required for synaptogenesis and neuronal circuit refinement [332]. In parallel, mitochondrial control of NAD^+/NADH ratios regulates the activity of sirtuin deacetylases, particularly SIRT1 and SIRT3, which coordinate histone deacetylation with neuronal energy demands and stress responses [333]. These pathways enable mitochondria to fine-tune epigenetic states in response to developmental cues and environmental inputs.

Mitochondria also influence epigenetic programming through one-carbon metabolism and mitochondrial–nuclear crosstalk. Mitochondrial folate and serine–glycine metabolism contribute to the generation of S-adenosylmethionine (SAM), the universal methyl donor for DNA and histone methylation[332]. Perturbations in mitochondrial metabolism can therefore lead to global or locus-specific hypomethylation or hypermethylation during critical windows of brain development. Additionally, retrograde signaling pathways transmit mitochondrial stress signals to the nucleus, reshaping transcriptional and epigenetic landscapes to adapt—or maladapt—to energetic insufficiency. Emerging evidence suggests that mitochondrial dynamics, including fission, fusion, and mitophagy, further regulate these processes by determining mitochondrial quality and metabolic output in neural stem cells [253,334] [333,251].

Collectively, these mechanisms position mitochondria as master regulators of epigenetic plasticity in the developing brain. By integrating metabolic status, redox balance, and signaling pathways, mitochondria orchestrate the epigenetic transitions necessary for orderly neurodevelopment. Disruption of mitochondrial function during early life can therefore lead to persistent epigenetic reprogramming, contributing to neurodevelopmental disorders, including developmental and epileptic encephalopathies, through long-lasting effects on neuronal identity, connectivity, and excitability.

Mitochondria-driven epigenetic regulation is particularly important for understanding the pathogenesis of PMD and DEE because it provides a unifying mechanistic framework linking early metabolic dysfunction to persistent neurodevelopmental and epileptic phenotypes.

In PMD, pathogenic variants in nuclear or mitochondrial genes directly impair oxidative phosphorylation, redox balance, and intermediary metabolism during critical windows of brain development. These impairments alter the availability of epigenetic substrates and cofactors—such as acetyl-CoA, α-ketoglutarate, NAD^+, and S-adenosylmethionine—leading to aberrant DNA methylation and histone modification patterns in neural progenitors [335]. Because epigenetic states established during embryonic and early postnatal development are relatively stable, early mitochondrial dysfunction can imprint long-lasting transcriptional programs that disrupt neuronal differentiation, cortical circuit assembly, and synaptic maturation [336–338]. This helps explain why many PMDs present with early onset, pharmacoresistant seizures and global developmental impairment that are disproportionate to structural neuroimaging abnormalities.

In DEE, even when the primary genetic defect lies in ion channels, synaptic proteins, or transcriptional regulators, recurrent seizures and network hyperexcitability impose extreme

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bioenergetic stress on neurons. This secondary mitochondrial dysfunction feeds back onto epigenetic regulation through ATP depletion, oxidative stress, altered NAD^+/NADH ratios, and disrupted one-carbon metabolism. Seizure-induced changes in mitochondrial metabolism can therefore reshape chromatin states, reinforcing maladaptive gene expression programs that favor hyperexcitability, impaired synaptic plasticity, and arrested cognitive development [336]. This mechanism provides a molecular explanation for the concept of "epileptic encephalopathy," in which epileptic activity itself contributes causally to developmental deterioration.

Importantly, mitochondrial epigenetic regulation helps explain the bidirectional and convergent relationship between PMD and DEE. In PMD, primary metabolic failure drives epigenetic dysregulation that predisposes to epilepsy and neurodevelopmental impairment. In DEE, sustained epileptic activity induces secondary mitochondrial and epigenetic reprogramming that stabilizes disease severity and limits developmental recovery. Both conditions therefore converge on shared downstream pathways involving chromatin remodeling, impaired neuronal fate specification, and persistent network dysfunction, despite distinct upstream genetic etiologies.

Clinically and therapeutically, this framework has major implications. It suggests that seizures and developmental deficits in PMD and DEE are not only acute electrical or metabolic phenomena but are maintained by long-lasting epigenetic programming. This may explain the limited efficacy of conventional ASMs and highlights the potential value of metabolic therapies (e.g., ketogenic diet, NAD^+ modulation), antioxidant strategies, and emerging epigenetic-targeted interventions. More broadly, viewing mitochondria as central epigenetic regulators reframes DEE and PMD as disorders of disrupted developmental programming, offering new avenues for disease modification rather than solely symptomatic seizure control.

11. Emerging Therapeutic Development for DEE

In addition to gene therapy for the disease-causing genes, mitochondria represent an emerging therapeutic target in DEE because they sit at the intersection of neuronal energy metabolism, redox balance, calcium homeostasis, and apoptosis regulation—processes that are profoundly disrupted in DEE. Developing neurons are uniquely vulnerable to mitochondrial dysfunction due to their high bioenergetic demands during periods of rapid growth, synaptogenesis, and circuit refinement [339]. Both primary mitochondrial defects and secondary mitochondrial injury driven by recurrent seizures can impair OxPhos, reduce ATP availability, and ROS, thereby lowering seizure threshold and exacerbating neurodevelopmental impairment. Targeting mitochondrial pathways therefore offers a strategy to intervene not only at the level of seizure control but also at the broader mechanisms underlying developmental stagnation and regression.

11.1. Enhancing Mitochondrial Bioenergetics

Therapies aimed at improving mitochondrial energy production represent one of the most established approaches in DEE. The ketogenic diet (KD) [340–343] is a prime example, inducing a metabolic shift toward fatty acid oxidation and ketone body utilization, which enhances mitochondrial efficiency and stabilizes neuronal networks. Pharmacologic strategies complement dietary interventions by supporting mitochondrial respiration through cofactors such as riboflavin or ETC bypass agents [344,345]. Anaplerotic substrates, which replenish TCA intermediates, also offer the potential to optimize ATP generation [336,346]. By bolstering bioenergetic capacity, these interventions can reduce seizure frequency, mitigate energy failure during ictal events, and support normal developmental trajectories in affected children.

11.2. Mitigating Oxidative Stress and Calcium Dysregulation

Drug treatments of oxidative stress and calcium dysregulation can be used to counteract the detrimental effects of neuronal hyperexcitability and the accompanying feed-forward loop. Mitochondria-targeted antioxidants aim to preserve mitochondrial integrity and prevent further

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degradation and cell apoptosis [347,348]. Stabilizing mitochondrial calcium homeostasis or preventing mitochondrial permeability transition further protects neurons from excitotoxic apoptosis and necrosis [275]. By reducing cumulative neuronal injury, these interventions not only improve seizure resilience but also help safeguard neurodevelopmental potential, which is critical in early childhood when neuronal networks are rapidly forming.

11.3. Targeting Mitochondrial Signaling and Quality Control

Beyond energy metabolism and oxidative stress, mitochondria influence long-term neurodevelopment through signaling and epigenetic mechanisms. Mitochondrial metabolites such as acetyl-CoA, NAD^+, and α-ketoglutarate modulate chromatin remodeling and gene expression programs essential for brain maturation. Therapeutic strategies that enhance mitochondrial biogenesis (e.g., activation of PGC-1α), optimize fission–fusion balance, or promote mitophagy offer the potential to correct maladaptive neuronal programming in DEE [288,349,350]. Coupled with precision medicine approaches that integrate genetic and metabolic profiling, these interventions may allow tailored mitochondrial-targeted therapies, transforming mitochondria from passive victims of epileptic stress into active drivers of disease modification and improved neurodevelopmental outcomes.

11.4. Mitochondrial Transplant Therapy

Mitochondrial transplant therapy (MTT) is a potential intervention for mitochondrial dysfunction in DEE by supplementing dysfunctional mitochondria in affected cells. The concept involves isolating healthy, functional mitochondria (often from autologous sources such as muscle or stem cells [351]) and delivering them to target tissues, including neurons, via direct injection, systemic administration, or cellular carriers. In preclinical models, transplanted mitochondria can integrate into host cells, restore ATP production, reduce oxidative stress, and improve calcium handling, thereby rescuing cellular bioenergetics and viability [352,353]. These effects suggest that MTT could mitigate the dual issues of energy failure and oxidative damage seen in DEE, particularly in cases with primary mitochondrial defects or severe seizure-induced mitochondrial injury.

Mechanistically, MTT may influence both acute and chronic neuronal outcomes. Acutely, the introduction of functional mitochondria can normalize ATP levels and reduce excitotoxic vulnerability during seizures [352,354]. Chronically, transplanted mitochondria may support neurodevelopment by stabilizing metabolic signaling pathways, reducing ROS-mediated DNA and protein damage, and potentially modulating epigenetic programs that are sensitive to mitochondrial metabolites [354,355]. These multifaceted effects make MTT a uniquely holistic approach, addressing not only seizure activity but also the underlying developmental impairments characteristic of DEE.

Despite its promise, mitochondrial transplant therapy remains largely experimental in the context of neurological disorders. Challenges include ensuring efficient mitochondrial uptake by target neurons, avoiding immune activation, and achieving long-term integration and function in the highly dynamic neural environment. Current research is focused on optimizing delivery methods, such as intrathecal injection, nanoparticle carriers, and stem cell-based mitochondrial transfer, and on demonstrating efficacy and safety in relevant preclinical models of epilepsy and neurodevelopmental disorders [352].

As MTT technology advances, it holds the potential to transform the treatment landscape for DEE, offering a precision, mechanism-based intervention that directly addresses mitochondrial dysfunction. By complementing existing metabolic, pharmacologic, and antioxidant therapies, mitochondrial transplantation may one day provide a path toward not only seizure control but also neurodevelopmental preservation and disease modification in children with DEE.

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Wu: Conceptualization, Project administration, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing.

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