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Review Article

Developmental and epileptic encephalopathies: etiology, diagnostic advances, and evolving management- a narrative review.

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ABSTRACT
Developmental and epileptic encephalopathies (DEE) comprise a severe spectrum of early-onset epilepsy syndromes where epileptic activity aggressively drives progressive cognitive and neurological regression beyond the underlying pathology. This narrative review evaluates the expanding genetic architecture of DEE, explores modern diagnostic developments, and outlines the ongoing paradigm shift from conventional symptomatic management toward gene-targeted, precision therapeutic strategies. A comprehensive literature search was conducted across major databases for articles published between 2010 and 2026.
Recent breakthroughs in next-generation sequencing have dramatically escalated diagnostic yields, allowing clinicians to identify pathogenic variants earlier and establish refined genotype-phenotype correlations. This molecular precision has opened doors for novel mechanism-based interventions, including antisense oligonucleotides, gene replacement platforms, and mutation-specific pharmacology. Concurrently, artificial intelligence-driven electroencephalography analytics and wearable multimodal monitoring networks are improving real-time seizure mapping and patient safety. However, widespread clinical implementation remains restricted by intense genetic heterogeneity, uncertain long-term safety records, and steep financial barriers.
Ultimately, incorporating genomic diagnostics into standard practice is transforming the clinical trajectory of DEE. Future research must prioritize multi-center clinical trials to validate long-term therapeutic efficacy and optimize early-intervention windows during critical stages of neuroplasticity.

***Keywords**: Developmental and epileptic encephalopathies; Epilepsy genetics; Electroencephalography; Neuroimaging; Precision medicine*
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Introduction
Epileptic encephalopathies (EE), now encompassed within the broader category of developmental and epileptic encephalopathies (DEE) by the International League Against Epilepsy (ILAE), represent a group of severe epilepsy syndromes in which epileptic activity itself, including both seizures and interictal epileptiform discharges, contributes to progressive cognitive, behavioral, and neurological impairment beyond the effects of the underlying etiology [1]. Core syndromes include Ohtahara syndrome, early myoclonic encephalopathy, West syndrome (infantile spasms), Dravet syndrome, Lennox–Gastaut syndrome, and Landau–Kleffner syndrome [2].
DEE is associated with significant morbidity and mortality and typically presents in early life, most commonly during the neonatal or infantile period. Neonatal-onset seizures carry the highest risk of severe developmental impairment, with a reported median age of onset of approximately 15 months [3,4]. These disorders frequently result in long-term neurodevelopmental deficits, including intellectual disability, autism spectrum disorder, and behavioral disturbances, reflecting their profound impact on the developing brain [3].
The etiological spectrum of DEE is highly heterogeneous, encompassing genetic, structural, metabolic, and other causes. Among these, genetic etiologies account for a substantial proportion of cases, particularly in early-onset epileptic encephalopathies. Approximately 50% of infants presenting with seizures before three months of age have an identifiable genetic cause, followed by structural abnormalities (~20%), metabolic disorders (~14%), and unknown etiologies [5]. Advances in genomic technologies, including targeted epilepsy panels, whole-exome sequencing, and whole-genome sequencing, have significantly improved diagnostic yield, reaching up to 70% in some cohorts [5,6]. These developments have enabled earlier and more accurate identification of pathogenic variants and have expanded understanding of the molecular

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mechanisms underlying epileptogenesis and neurodevelopmental dysfunction.

Early and accurate diagnosis remains critical, as some metabolic epilepsies, such as pyridoxine-dependent epilepsy, biotinidase deficiency, and folinic acid-responsive seizures, are potentially reversible if detected promptly [5]. In addition to genetic and metabolic causes, inflammatory and infectious pathways also contribute to early-onset epileptic encephalopathies. Febrile infection–related epilepsy syndrome (FIRES), for example, is characterized by the abrupt onset of refractory seizures following a febrile illness in previously healthy children and is often associated with poor long-term outcomes [7]. Neuroimaging plays an essential role in these contexts, with magnetic resonance imaging and advanced techniques such as diffusion-weighted imaging and magnetic resonance spectroscopy aiding in the detection of structural and metabolic abnormalities, particularly in infection-related encephalopathies [8].

Despite advances in diagnostic technologies and supportive care, clinical outcomes remain poor for many DEE subtypes. Significant early mortality is observed in STXBP1-related disorders, with respiratory infections and sudden unexpected death in epilepsy (SUDEP) representing major causes of death [9]. Similarly, WWOX-related DEE is associated with severe structural brain abnormalities and very early seizure onset with significantly lower survival rates, particularly among patients with bi-allelic loss-of-function variants [10].

Electroencephalography (EEG) remains the cornerstone of diagnostic evaluation and syndromic classification in DEE. Advanced modalities, including quantitative EEG and continuous EEG monitoring, provide objective measures of cerebral dysfunction and enable real-time seizure detection, thereby improving diagnostic accuracy and clinical management [11]. Functional imaging techniques, such as fluorodeoxyglucose positron emission tomography (FDG-PET) and ictal single-photon emission computed tomography (SPECT), can provide additional insights in cases where conventional imaging and EEG findings are inconclusive [12].

Despite advances in diagnostic technologies, the management of DEE remains challenging. Conventional antiseizure medications often provide only partial seizure control, and pharmacoresistance is common. Furthermore, seizure reduction does not necessarily prevent ongoing developmental impairment, highlighting the need for therapies that address the underlying disease mechanisms. Management, therefore, requires a multidisciplinary approach that also targets associated comorbidities, including intellectual disability, autism spectrum disorder, and movement disorders [13].

Recent advances in molecular genetics have begun to transform the therapeutic landscape of DEE. Improved understanding of gene-specific pathophysiology has enabled the development of precision medicine approaches aimed at targeting underlying genetic defects. Emerging therapeutic strategies, including antisense oligonucleotides, gene replacement therapies, and mutation-specific pharmacological interventions, offer the potential to modify disease progression rather than solely suppress seizures. Although these approaches remain in early stages of clinical application, they represent a promising shift toward individualized and mechanism-based treatment.

Given the clinical and etiological complexity of DEE and the rapid evolution of genetic and therapeutic advances, a comprehensive understanding of these disorders is essential. This review aims to synthesize current evidence on the epidemiology, etiology, diagnostic approaches, and management of DEE, with a particular focus on emerging genomic technologies and gene-targeted therapies, to support improved clinical care and future research.

METHODOLOGY

Study Design

This study is a narrative review designed to synthesize, analyze, and critically evaluate the evolving medical literature regarding the genetic architecture, diagnostic advances, and emerging precision therapies for developmental and epileptic encephalopathies (DEE).

Databases, Filters, Years, and Language Considered

A comprehensive search of electronic databases—including PubMed, Scopus, and Google Scholar—was conducted. Automated filters and manual checks were used to restrict results to papers published in the English language. To capture the most relevant contemporary advances while grounding the review in core historical milestones, literature published between the specific years of 2010 and 2026 was prioritized.

Inclusion and Exclusion Criteria

- **Inclusion Criteria:** Peer-reviewed original research articles, prospective observational studies, multi-center clinical trials, cohort studies, and high-quality review papers focusing directly on the genetic basis of DEE, next-generation sequencing diagnostic yields, genotype-phenotype correlations, and modern targeted therapeutics (e.g., ASOs, gene therapies, and precision pharmacology).
- **Exclusion Criteria:** Studies outside the specified timeline (unless deemed seminal historical literature), articles published in languages other than English, single-patient case reports with low generalizability, and papers lacking a clear focus on the molecular, electroclinical, or diagnostic landscapes of epileptic encephalopathies.

Search strategies utilized combinations of Boolean operators (AND, OR) alongside targeted keywords:

"developmental and epileptic encephalopathy," "genetic epilepsy," "epileptic encephalopathy," "precision medicine," "gene therapy," "antisense oligonucleotides," "genomic diagnostics," and "next-generation sequencing."

DISCUSSION

Etiology

The epileptic encephalopathy (EE) triad comprises refractory seizures, epileptiform activity on electroencephalogram (EEG), and detrimental effects on development, cognition, and often behavior [14]. Pre-existing developmental delays or intellectual disabilities attributed to a non-progressive brain condition are known as developmental encephalopathies (DEEs), and as the brain matures, the severity of the disability may become more evident [15]. Individuals with DEs are more likely than the general population to have epilepsy, suggesting that the underlying cause of their epilepsy is directly accountable for developmental delays [15]. A collection of severe neurological conditions known as Developmental Epileptic Encephalopathies (DEEs) combines EEs with DEs, resulting in a complex clinical presentation that includes seizures, developmental delays, and cognitive deficits [16].

The International League Against Epilepsy (ILAE) Task Force on Nosology and Definition's most recent suggestion for the classification of epilepsy syndromes is incorporated in the table below, which illustrates the spectrum of DEEs by age of onset [17-19]. This paradigm emphasizes a continuum of self-limited epilepsy syndromes of infancy to more severe developmental and epileptic encephalopathies that have devastating neurodevelopmental outcomes (Table 1, Table 2).

Table No. 1: Self-Limited and Variable-Age Onset Epilepsy Syndromes in Infancy and Childhood.

Syndrome / Category (Reference)	Age of Onset	Seizure Type / Features	EEG Findings	Developmental / Comorbid Features
Self-limited (familial) neonatal epilepsy*(Zuberi et al., 2022)*	Days 2–7	Focal tonic features at onset (head, face, limbs); can progress to bilateral tonic-clonic seizures.	Initial EEG attenuation (up to 20 sec), recurrent centrotemporal spike discharges; bilateral/ asynchronous.	Mostly normal development; occasional mild motor or learning difficulties.
Self-limited familial neonatal-infantile epilepsy (SeLFNIE)*(Zuberi et al., 2022)*	1 day – 23 months	Head/ocular deviation, focal tonic clonic, possible bilateral tonic-clonic.	Normal background; occasional focal or generalized slowing.	Seizures cease by age 1–2 years; normal long-term neurodevelopment.
Self-limited (familial) infantile epilepsy (SeLIE)*(Zuberi et al., 2022)*	3–20 months *(peak: 6 months)*	Focal seizures: behavioral arrest, cyanosis, staring, automatisms, head/eye version, clonic movements; may progress to bilateral tonic-clonic.	Mostly normal interictal EEG; focal discharges localized to the temporal or posterior regions.	Seizures usually remit within 1 year; paroxysmal kinesigenic dyskinesia is possible in later childhood/adulthood.
Genetic epilepsy with febrile seizures plus (GEFS+)*(Zuberi et al., 2022)*	<6 months, may persist >6 years	Febrile seizures (focal/generalized), and other afebrile seizure types.	Normal background; occasional focal or generalized spike-wave complexes.	Seizures typically resolve spontaneously by puberty.

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Myoclonic epilepsy in infancy (MEI)*(Zuberi et al., 2022)*	<4 months or >3 years	Myoclonic seizures, mostly involving the head and upper arms, may be reflex-induced; febrile seizures occur in ~1/3.	Generalized spike-wave or polyspike-wave, prominent in early sleep; triggered by startle, sound, or touch.	Sometimes mild learning or attention deficits, moderate intellectual disability (ID) are observed in a minority of cases.
Rasmussen syndrome*(Riney et al., 2022)*	1 to 10 years	Childhood onset: Focal aware; Adult onset: Focal impaired awareness.	Polymorphic epileptiform abnormalities and progressive hemispheric slowing.	Progressive, severe neurological deficit and hemispheric atrophy.

Table No. 2: Severe Early-Onset Developmental and Epileptic Encephalopathies (DEEs) and Structural/Metabolic Syndromes

Syndrome / Category (Reference)	**Age of Onset**	**Seizure Type / Features**	**EEG Findings**	**Developmental / Comorbid Features**
Early-infantile developmental and epileptic encephalopathy (EIDEE)*(Zuberi et al., 2022)*	Birth – 3 months	Tonic or focal/multifocal myoclonus; epileptic spasms; high-frequency multiple daily seizures.	Burst-suppression, discontinuity, diffuse slowing, multifocal spikes, spike-waves; high-voltage bursts alternating with suppression.	Moderate to profound ID; movement disorders (tremor, dystonia, chorea); global neurological comorbidities; high early mortality.
KCNQ2-DEE*(Zuberi et al., 2022)*	<3 months	Focal tonic seizures accompanied by autonomic features, apnea, and ictal sobbing.	Asymmetric burst-suppression or multifocal sharp waves are common.	Moderate to severe permanent neurodevelopmental impairment.
Pyridoxine / Pyridox(am)ine 5'-Phosphate-dependent epilepsy*(Zuberi et al., 2022)*	First year of life	Intractable seizures starting in the first hours/days of life; may appear prenatally.	Continuous burst-suppression pattern or generalized slowing.	Severe developmental impairment if targeted treatment is delayed.
Epilepsy of infancy with migrating focal seizures (EIMFS)*(Zuberi et al., 2022)*	First 6 months *(mean: 3 months)*	Polymorphic tonic or focal motor-clonic seizures; prominent autonomic features; behavioral arrest.	Monotonous 4–10 Hz ictal activity with pathognomonic migrating multi-focal propagation across hemispheres.	Severe, progressive neurodevelopmental delay and regression.
Infantile epileptic spasms syndrome (IESS) *(Zuberi et al., 2022)*	1–24 months	Sudden axial tonic contractions (<3 sec), occurring in clusters;	Hypsarrhythmia: chaotic, high-amplitude, multifocal epileptiform discharges with	Profound risk of permanent neurodevelopmental

		can be flexor, extensor, or mixed.	disorganized background slowing; best seen in non-REM sleep.	regression and intellectual deficits.
Dravet syndrome (DS) *(Zuberi et al., 2022)*	1–20 months	Prolonged focal clonic (hemiclonic) or generalized clonic seizures, characteristically triggered by minor fever or warm water.	Background may be normal initially; later evolves to generalized, focal, or multifocal spike-wave discharges; photosensitive.	Developmental slowing noted 12–60 months post-onset; severe speech delay; 50% showcase mild-to-severe ID; hyperactivity.
CDKL5 / PCDH19-related DEE *(Zuberi et al., 2022)*	First year of life	Hypermotor tonic spasms evolving into a tonic phase (limb extension/flexion, vocalization, rocking, kicking).	Background EEG appears deceptively normal up to 4 months of age before deteriorating.	Concomitant hyperkinetic movement disorders in some cohorts; moderate-to-severe intellectual disability.
PCDH19 Encephalopathy *(Zuberi et al., 2022)*	Females: 1.5–60 mo Males: 5–96 mo	Brief, cluster-focal seizures with impaired awareness, tonic extension of arms, head/eye deviation, pallor, and fear-screaming.	Diffusely slow background with infrequent focal spikes; seizure clustering dramatically increases spike frequency.	Up to 70% present with Autism Spectrum Disorder (ASD); intellectual disability onset begins in the 2nd year and worsens after age 10.
Sturge-Weber syndrome*(Zuberi et al., 2022)*	First year of life	Focal motor or autonomic seizures; highly variable levels of consciousness.	Asymmetric voltage reduction and polymorphic slowing over the affected hemisphere.	Lifelong drug-resistant epilepsy, stroke-like hemiparetic episodes, glaucoma, and psychiatric comorbidities.
Gelastic seizures with hypothalamic hamartoma*(Zuberi et al., 2022)*	First year of life	Inappropriate, unprovoked laughter (gelastic events); highly frequent daily clusters.	Surface EEG is usually normal initially; deep subcortical discharges are missed without depth electrodes.	Severe cognitive decline and behavioral/developmental regression.
Lennox–Gastaut syndrome*(Specchio et al., 2022)*	<18 years	Polymorphic: Tonic (prominent in sleep), atypical absence, atonic (drop attacks), myoclonic, and nonconvulsive status.	Generalized slow spike-wave complexes (1.5–2.5 Hz) during wakefulness; paroxysmal fast activity (~10 Hz) during sleep.	Severe intellectual disability, treatment resistance, and a high injury profile from drops.
Hemiconvulsion–hemiplegia–epilepsy syndrome*(Specchio et al., 2022)*	<4 years	Acute phase: prolonged febrile hemiclonic status epilepticus followed by flaccid hemiparesis; Chronic phase: focal seizures.	Rhythmic slow waves (2–3 Hz) over the affected hemisphere; recruitment rhythms approaching 10 Hz during status.	High incidence of permanent drug-resistant epilepsy and spastic focal motor deficits (hemiplegia).

Diagnostic Evaluation of Epileptic Encephalopathy

Apart from clinical assessment, electroencephalography (EEG) is critical in identifying epileptic encephalopathy (EE), as it provides objective evidence of abnormal cerebral function and supports syndrome classification [20,21]. In EE, EEG typically shows marked or region-specific cerebral dysfunction [20,21,22]. A common finding across many EE syndromes is diffuse background slowing, characterized by reduced dominant frequencies, loss of the normal anterior–posterior gradient, impaired reactivity to sensory stimuli, and disrupted sleep architecture, all of which correlate with global cerebral impairment [22,21].

Several EE syndromes demonstrate distinctive EEG signatures. Ohtahara syndrome and early myoclonic encephalopathy are defined by a burst–suppression pattern, consisting of high-voltage bursts of spikes and sharp waves alternating with near-isoelectric suppression phases during both wakefulness and sleep [23–25]. West syndrome is characterized by hypsarrhythmia, a chaotic, high-amplitude EEG pattern with multifocal spikes and slow waves, strongly associated with neurodevelopmental delay [26,27]. In Dravet syndrome, the EEG is often normal at seizure onset but later evolves to generalized or focal epileptiform discharges, frequently with photosensitivity [28]. Lennox–Gastaut syndrome typically shows slow spike-and-wave complexes (1.5–2.5 Hz) during wakefulness and paroxysmal fast activity during sleep [22,26]. Electrical status epilepticus during sleep (ESES/CSWS) is defined by near-continuous bilateral spike-and-wave discharges occupying more than 85% of non-rapid eye movement sleep and is closely associated with cognitive and behavioral regression [29,30].

Brain scans like magnetic resonance imaging (MRI) augment EEG by uncovering structural and signal abnormalities as they pertain to epileptogenesis. Typical findings include hippocampal sclerosis, which includes hippocampal atrophy and increased T2/FLAIR signal intensity, and focal cortical dysplasia, which demonstrates cortical thickening, blurring of the gray–white matter junction, and subcortical white matter signal abnormalities [31–33]. Neuronal migration disorders, e.g., lissencephaly and heterotopia, are related to abnormal cortical development and are a common early-onset cause of EE [31,33]. In acute infection-induced encephalopathies, delayed subcortical diffusion restriction and cortical or white matter signal changes could be detected by MRI analysis, which provide important diagnostic and prognostic information. Genetic testing has become a cornerstone of EE evaluation, especially in early-onset, pharmacoresistant epilepsy or cases where developmental regression is present. Next-generation sequencing (NGS) methods, such as epilepsy gene panels and whole-exome sequencing, demonstrate pathogenic variants in a significant percentage of EE cases and play an important role in ESES-associated encephalopathies where monogenic determinants like KCNQ2, KCNA2, and GRIN2A are commonly implicated [29,34,35]. Identification of causative variants informs prognosis, enables targeted therapy, and supports accurate genetic counseling [36].

Accurate diagnosis of epileptic encephalopathy and personalized management strategies are critically dependent on an integrative diagnostic platform, integrating clinical manifestations, EEG activity patterns, neuroimaging, and genomic studies.

Neuroimaging

Imaging techniques, especially magnetic resonance imaging (MRI), are central in the characterization of both structural and pathological underpinnings of epileptic encephalopathies (EE). Some MRI imaging abnormalities include structural changes indicative of chronic epileptogenic processes and neurodevelopmental disruption. Such hippocampal sclerosis is a common finding in temporal lobe epilepsy, with hippocampal atrophy accompanied by increased T2/FLAIR signal, loss of internal architecture, and secondary enlargement of the temporal horn, frequently related to prolonged or refractory phase of seizures [31,32,37].

Focal cortical dysplasia (FCD) represents another major epileptogenic substrate, especially in children with drug-resistant epilepsy. MRI features include cortical thickening, blurring of the gray–white matter junction, subcortical white matter hyperintensities, and the transmantle sign, in which abnormal signal extends radially toward the ventricle [33,38]. Malformations of cortical development, such as lissencephaly, pachygyria, and heterotopia, arise from abnormal neuronal migration and are marked by altered cortical thickness, reduced gyration, and ectopic gray matter nodules, contributing significantly to early-onset epileptic syndromes [33,39].

Diffuse or regional cerebral atrophy is commonly observed in chronic or progressive epileptic encephalopathies and reflects extensive neuronal loss, often correlating with cognitive decline. Additionally, cortical and subcortical T2/FLAIR signal abnormalities may indicate gliosis, inflammation, or ongoing seizure-related injury [32,39]. In infection-triggered encephalopathies, characteristic MRI patterns such as delayed subcortical diffusion restriction (“bright tree appearance”) and cortical hyperintensities may be seen, depending on the underlying infectious or inflammatory etiology [39]. Collectively, these neuroimaging features assist in localization, etiological classification, and prognostication in EE.

Genetic and Metabolic Testing

Genetic and metabolic analyses have increased the frequency and extent of epilepsy, highlighting the relevance of ESES in the differential diagnosis of monogenic developmental and epileptic encephalopathies. Over 20% of

DEE/EE patients with ESES present pathogenic or likely pathogenic variants, emphasizing the role genetic factors play. Genes often implicated in the same are the ion channel genes KCNQ2 and KCNA2, and glutamate receptor genes GRIN2A [29,34,40]. KCNQ2-related encephalopathy shows considerable phenotypic heterogeneity, including benign familial neonatal seizures to profound early-onset epileptic encephalopathy, with some patients developing ESES later [40,41]. Likewise, KCNA2 loss-of-function variants are linked to a spectrum from low levels of epilepsy to severe encephalopathy that may progress to ESES with age [34]. Mutation in GRIN2A has been strongly linked to epilepsy–aphasia spectrum disorders and ESES, with a probable pathogenesis being disruption of glutamatergic signaling during critical windows of postnatal neuroplasticity [34,35]. Next-generation sequencing (NGS) plays an essential role in the enhancement of diagnostic yield for epilepsy. Pathogenic variants in a substantial proportion of epilepsy patients, especially those with early-onset seizures and developmental delay, are identified in targeted epilepsy gene panels and exome sequencing [36]. Common genes are PRRT2-, SCN1A-, and TSC2-associated. Mutations in PRRT2 are well-known correlates of benign familial infantile epilepsy, and SCN1A mutations cause Dravet syndrome in part due to disturbed GABAergic inhibition [36]. A mutation in TSC2 results in mTOR pathway activation that contributes to epileptogenesis and is a basis for mTOR-targeted treatments like everolimus [36].
Incorporating Diagnostic Data
Matching the clinical features, EEG, neuroimaging findings, and genetic data is essential for the accurate diagnosis of EE. The integrated approach allows for accurate syndrome categorization, prognosis, and individual treatment strategies.

Management Overview

Management of acute seizure involves stabilization, elimination of reversible conditions, and initiation of anti-seizure medications at the earliest possible opportunity. Phenobarbital is still first-line therapy in neonatal seizures, but levetiracetam has been used more and more as a second-line agent, with improved tolerability [42]. Antivirals like acyclovir and antibiotics should be started at an early stage in suspected infectious encephalitis [43]. Precise medicine is a new strategy used to handle DEE. Modern anti-seizure drugs, dietary ketogenic therapies, and surgery for epilepsy are still the cornerstone of treatment options, while genotype-specific therapies - such as sodium channel blocking against gain-of-function SCN2A/SCN8A variants or mTOR inhibitors in TSC2-linked epilepsy - provide a more accurate and systematic approach [44,45]. Antisense oligonucleotide therapy, gene therapy, and neuromodulation have further paved the way to mechanism-based treatment schemes for epilepsy encephalopathies [44,46].
New and adjunctive strategies for the treatment of developmental and epileptic encephalopathies of childhood and epilepsy. Beyond more traditional treatments and anti-seizure agents, such as ketogenic medicine, which consists of anti-seizure medications and surgery for epilepsy, there is increasing concern for adjunctive and disease-modifying strategies for developmental and epileptic encephalopathies (DEEs). These efforts are developed on the basis of not just the treatment of seizures, but mechanisms that provide relief from neuronal injury, regulate epileptogenic networks, and modulate underlying molecular pathways. The development of new therapeutic strategies also includes neuroprotective drugs, gene- and oligonucleotide-based therapies, and monitoring systems for this specific area of concern, which are based on technology.

The use of neuroprotective strategies in adjunctive therapy

Oxidative stress, mitochondrial dysfunction, excitotoxicity, and neuroinflammation that contribute to epileptogenesis and the neuronal injury induced by seizures are major drivers of both epileptogenesis and seizure-induced damage related to epilepsy. In DEEs, the recurrent seizure cycle has a strong component where ongoing neurodevelopment meets these processes. Curcumin also shows neuroprotective power using experimental epilepsy models. Consequently, supplementation with curcumin in chronic epilepsy paradigms enhanced mitochondrial function and attenuated behavioral impairments, primarily due to decreased ROS, stabilization of mitochondrial membrane, and attenuation of lipid peroxidation, in chronic epilepsy paradigms [47]. Curcumin may exert some degree of anti-epilepsy, reducing the potential contribution of neurodegenerative stress pathways, reducing the brain region over the course of therapy, and improving the brain's ability to handle seizure-related cognitive decline, but its clinical applications are restricted by bioavailability [47]. Coenzyme Q10 (CoQ10) is a further, mitochondrial-bound substance with anti-apoptotic and antioxidant activity. Experiments have shown that CoQ10 inhibits mitochondrial depolarization and apoptosis apart from its free radical scavenging capabilities [48]. In neuron-depolarized hippocampal slice cultures that had undergone excitotoxic insult, CoQ10 limited the loss of neurons and protected against kainate-induced nervous system damage [49]. Since mitochondrial apoptotic signaling directly contributes to neuronal loss in temporal lobe epilepsy, and particularly to the post-status epilepticus local environment in the CA3 hippocampal subfield [50], mitochondrial stabilizers like CoQ10 represent mechanistically rational adjuncts. Yet, an indiscriminate suppression of ROS by high-dose antioxidants may interfere with physiological redox signaling. Such problems point to an underutilization of certain redox molecules for others. Metformin, widely used for type 2 diabetes, has also developed into a therapeutic agent recently due to its anti-inflammatory and anti-apoptotic effects. Through activation of AMP-activated protein kinase (AMPK) and inhibition of the mTOR

pathway, metformin has anti-inflammatory and anti-apoptotic functions. In models of epilepsy challenged by metabolic dysfunction in the laboratory, metformin decreased pro-inflammatory cytokines and improved cognitive outcomes [51]. Wider results indicate possible advantages of metformin in epilepsy and associated neurodegenerative diseases through modulation of cellular metabolism and autophagy circuits [52]. However, the penetration into the CNS at standard dosages remains an ongoing issue, and gastrointestinal intolerance and vitamin B12 deficiency are potential side effects. Puerarin, an isoflavone isolated from Pueraria lobata, has shown antioxidant and anti-apoptotic properties in seizure models. Puerarin increases pilocarpine-induced epilepsy Bcl-2 expression, reduces Bax expression, and preserves mitochondrial membrane potential in the hippocampus, thereby limiting neuronal death [53]. It also attenuated neuroinflammation and oxidative injury in toxin-induced models [54]. Despite promising preclinical data, limited solubility and bioavailability restrict its clinical applicability.

Thymoquinone, the principal bioactive ingredient of Nigella sativa, has also demonstrated neuroprotection in the same manner. In vitro and in vivo studies show thymoquinone reduces endoplasmic reticulum stress, apoptotic pathways, mitochondrial dysfunction, and excitotoxic damage due to its action on endoplasmic reticulum stress, decreasing cellular apoptotic events [55]. Protective effects against toxin-induced neuronal damage further support its anti-apoptotic potential [56]. Although these phytochemicals have promise mechanistically, robust clinical trials are necessary to establish the safety, efficacy, and pharmacokinetics of the drug in pediatric cohorts suffering from DEEs. Levetiracetam (LEV), a type of anti-seizure drug, plays the role of a neuroprotective agent. LEV interacts with synaptic vesicle glycoprotein 2A (SV2A) and modulates synaptic vesicle exocytosis and neurotransmitter release [57]. Aside from mitigating seizure frequency, LEV is a candidate for oxidative stress reduction and for calcium dynamics modulation in vitro [58]. In a multicenter RCT of high-dose LEV monotherapy in refractory partial seizures, a meaningful reduction in seizure frequency was seen with a large magnitude for the treatment of refractory partial seizures, establishing both benefit and a tolerability profile [59]. Behavioral side effects such as irritability and mood changes are still clinically applicable. Together, neuroprotective agents represent a paradigmatic move to further focus on the destruction routes of secondary injury through which DEEs occur. Nevertheless, most of the data are preclinical, and translational lags need to be covered before they can be incorporated as routine elements of the treatment algorithms.

Gene and Oligonucleotide Therapies

The realization that several DEEs are monogenic has spurred efforts towards precision gene-based therapies. These approaches also seek to correct, silence, or compensate for pathogenic variants to address the pathophysiological cause of disease. Such RNA interference (RNAi)-based strategies have been studied in models of epileptic encephalopathy related to DNM1. De novo mutations in synaptic transmission genes, such as DNM1, affect synaptic vesicle endocytosis and are associated with severe early-onset epilepsy [60]. In a genetic mouse model and microRNA targeting mutant Dnm1a using adeno-associated viral vectors, pathogenic mRNA expression was reduced significantly in order to significantly increase survival and seizure outcomes [61]. This is the first indication of proof-of-concept for allele-specific gene silencing in DEEs. Another gene therapy approach targeted neuromodulators that are inhibitory. A lentiviral vector expressing both neuropeptide Y (NPY) and its Y2 receptor under an excitatory neuron–specific promoter reduced seizure frequency in rodent models under tight video-EEG monitoring [61]. The potential for neuroprotective effects following activation of the NPY receptor has been related to its efficacy against glutamate-induced excitotoxicity [62], indicating both anti-seizure and neuroprotective potential. Antisense oligonucleotides (ASOs) are a particularly promising therapeutic modality for monogenic epilepsies. ASOs are short synthetic nucleic acid sequences targeted to modulate RNA expression. Studies in KCNT1-related DEE experimental models demonstrated the capacity to significantly reduce expression of mutant transcripts, nearly abolish seizures, and increase survival following intracerebroventricular delivery of a targeted ASO [63]. Wider investigations highlight the increasing effectiveness of ASOs for targeted treatments of multiple genetic epilepsies [64]. Early-phase data are promising, but challenges remain in delivery modality, durability of effect, immune responses, and long-term safety.

Gene and oligonucleotide therapies signify a paradigm shift from symptomatic seizure suppression toward disease modification. Ethical considerations, cost, and equitable access remain critical issues as these therapies transition from bench to bedside.

Artificial Intelligence and Advanced Monitoring

This paper highlights the growing evidence that accurate seizure screening and phenotyping are key to optimizing treatment and safely treating patients with DEEs, who tend to have frequent or nocturnal seizures. In fact, machine learning (ML) and deep learning models are capable of automatically detecting seizures from electroencephalographic (EEG) data, diminishing dependence on human-interpretation steps [65]. Wearable sensors such as wrist accelerometers and multimodal devices have been used extensively in multicenter prospective studies to detect generalized tonic-clonic seizures [66]. Benchmark studies with wearable sensors and ML algorithms show enhancement of sensitivity and

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specificity but vary among types of seizures [67]. These consist of variability of signals, inconsistent device placement, and a decrease in accuracy over non-motor seizures. Video-based seizure detection systems offer complementary benefits. For convulsive and hyperkinetic seizures, automated nocturnal video analysis in pediatric populations has produced high detection rates along with low false detection frequencies [68]. The feasibility of these systems for long-term monitoring has also been demonstrated in residential care settings [69]. In the future, the incorporation of multimodal streams of data—EEG, accelerometry, and video—may improve the detection accuracy; these data streams can allow for closed-loop therapeutic interventions. In epilepsy phenotyping, artificial intelligence is increasingly promising for large-scale analysis of clinical, imaging, and genomic data to spot subgroups and to predict future outcomes. However, the implementation of such systems must overcome problems like data standardization, algorithm transparency, and clinical validation before widespread application.

Limitations and Quality of Reviewed Research

While this review captures rapid, high-impact breakthroughs in genetic profiling and precision therapeutics, several systemic limitations persist within the reviewed literature. First, the vast majority of advanced neuroprotective pharmacology (e.g., curcumin, thymoquinone, puerarin) and gene-silencing models (e.g., ASO platforms for KCNT1) remain restricted to preclinical rodent paradigms or in vitro slice cultures. Significant translational gaps exist regarding delivery mechanics across the human blood-brain barrier, metabolic durability, and optimal dosage tolerability in pediatric patient populations.

Second, clinical diagnostic studies regarding next-generation sequencing and digital healthcare monitoring suffer from sample size constraints and geographical selection biases. Many registry cohorts represent specialized, high-resource tertiary epilepsy centers, which potentially inflates reported diagnostic yields and overrepresents accessible socioeconomic groups. Finally, long-term safety records and large-scale efficacy data regarding both artificial intelligence monitoring algorithms and genetic replacement platforms remain low, underscoring the preliminary nature of these precision medicine frameworks.

Conclusion

Developmental and epileptic encephalopathies (DEE) represent a clinically and etiologically heterogeneous group of disorders with significant neurological and developmental consequences. Advances in genomic technologies have substantially improved the identification of underlying genetic causes, enabling earlier and more precise diagnoses. This evolving understanding has shifted the conceptual framework of DEE from predominantly electroclinical syndromes to genetically defined disorders with distinct pathophysiological mechanisms.

Importantly, these insights are driving a transition from conventional symptomatic management toward mechanism-based and precision therapeutic approaches. Emerging strategies, including gene-targeted therapies, antisense oligonucleotides, and precision pharmacological interventions, offer promising avenues for modifying disease progression rather than solely controlling seizures. Early clinical applications have demonstrated encouraging results in selected genetic subtypes, underscoring the potential of personalized treatment approaches in improving outcomes.

However, several challenges remain. The marked genetic and phenotypic heterogeneity of DEE, limited availability of targeted therapies, high costs, and insufficient long-term safety and efficacy data continue to restrict widespread clinical implementation. In addition, optimizing timing of intervention—particularly in early developmental windows—remains a critical consideration.

Future efforts should focus on expanding access to comprehensive genomic testing, advancing translational research, and conducting robust clinical trials to evaluate emerging therapies. A multidisciplinary approach integrating neurology, genetics, neurophysiology, and rehabilitation will be essential to address the complex needs of affected individuals.

In conclusion, while significant challenges persist, the integration of molecular genetics into clinical practice is reshaping the landscape of DEE, offering new opportunities for precision medicine and improved patient outcomes.

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List of Abbreviations:

- AMPK AMP: activated protein kinase
- ASO: Antisense oligonucleotide
- CBME: Competency-Based Medical Education
- CNS: Central Nervous System
- CoQ10 : Coenzyme Q10
- CSWS: Continuous Spike and Wave during Sleep
- DEE: Developmental and Epileptic Encephalopathy
- EEG: Electroencephalography
- EIDEE: Early-Infantile Developmental and Epileptic Encephalopathy
- EIMFS: Epilepsy of Infancy with Migrating Focal Seizures
- ESES: Electrical Status Epilepticus during Sleep
- FCD: Focal Cortical Dysplasia

- FDG-PET: Fluorodeoxyglucose Positron Emission Tomography
- FIRES: Febrile Infection–Related Epilepsy Syndrome
- IESS: Infantile Epileptic Spasms Syndrome
- ILAE: International League Against Epilepsy
- LEV: Levetiracetam
- ML: Machine Learning
- MRI: Magnetic Resonance Imaging
- NGS: Next-Generation Sequencing
- NPY: Neuropeptide Y
- ROS: Reactive Oxygen Species
- SPECT: Single-Photon Emission Computed Tomography
- SV2A: Synaptic Vesicle Glycoprotein 2A

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Author Contributions
This research work was a collaborative work of all authors, ranging from data collection to the overall manuscript assembly and finalization.

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