# Deciphering Developmental Epileptic Encephalopathies (DEE): Unravelling the Key Signs

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## Abstract

**Background:** Epilepsy, a chronic neurological disorder affecting over 50 million people worldwide, is marked by recurrent seizures and loss of consciousness. It is categorized based on EEG features, etiologies, and comorbidities. Developmental Encephalopathy (DE) involves developmental delays and early-onset seizures without causing developmental regression. In contrast, Epileptic Encephalopathy (EE) features severe epilepsy syndromes where frequent seizures result in developmental delays or regression.

**Methods:** This review explores the clinical definitions, epidemiology, and diagnostic criteria for DE, EE, and DEEs. It covers their etiologies, clinical features, diagnostic methods, and treatment strategies, including genetic, structural, metabolic, and immune-related factors.

**Results:** DE features developmental impairment with epilepsy, while EE involves severe epilepsy causing cognitive and behavioral dysfunction. DEEs are marked by early-onset severe epilepsy and EEG abnormalities that worsen developmental impairments. Essential diagnostic tools include EEG, neuroimaging, and genetic testing. Effective management requires personalized interventions to control seizures and address cognitive deficits.

**Conclusion:** DEEs are a complex epilepsy subset with major developmental and cognitive challenges. Early diagnosis and targeted treatments are crucial for improving outcomes. Ongoing research into DEEs' genetic and pathophysiological mechanisms is key to enhancing understanding and management.

## Introduction

Epilepsy is a chronic disease of the brain that has affected more than 50 million people worldwide. Recurrent seizures, episodes of involuntary movements, and loss of consciousness are the characteristics of patients suffering from epilepsy. Epilepsy can be grouped and typed into different categories based on its EEG features, etiologies, and comorbidities.[1]

The International League Against Epilepsy (ILAE) task force in 2014 propose the clinical definition of epilepsy defined by any of the following conditions.[2]

1. At least two unprovoked (or reflex) seizures occurring >24 h apart.
2. One unprovoked (or reflex) seizure and a probability of further seizures like the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years.
3. Diagnosis of epilepsy syndrome.

The incidence of epilepsy varies between countries. The estimated incidence that could be found in developing countries is 187/100,000. Recent study has also revealed the maximum incidence occurs in the first year of age is 102/100,000 cases per year. In children from the age of 11 to 17 years old, the incidence is 21-24/100,000 cases per year.[3]

Developmental Encephalopathy (DE) is a heterogenous group of epilepsy subtype with the characteristics of developmental impairment with early onset. DE has been related with other neurological symptoms such as autonomy dysfunction, behavioral disorder, and motor impairment. The prominent feature that can be observed in patients suffering from DE is the delay in development, whereas epileptic activity does not appear to be associated with the developmental delay, regression, or stagnation.[4]

Meanwhile Epileptic Encephalopathy (EE) is another subtype of heterogenous group involving syndromes of severe epilepsy syndrome. EE is characterized with several types of seizure, frequent epileptiform activity on EEG, with developmental delay or regression. On EE, there is no history of developmental delay on pre-existing condition that could be found. But on the other hand, developmental delays that can be observed on EE happened because of disruption on brain physiological process regarding to frequent epilepsy activity.[5]

However, in some cases of severe epilepsy in early onset of life, it is usually difficult to know whether the underlying cause of epileptic encephalopathy would be the only reason causing developmental delay even in the absence of epilepsy. So that the term Developmental and Epileptic Encephalopathies (DEEs) was designated to define a heterogenous group of disorder characterized by early-onset, often severe epileptic seizures, and EEG abnormalities on a background of developmental impairment that tends to be worsen as a sequalae of epilepsy.[6]

DEE condition refers to when cognitive functions are influenced by seizures and interictal epileptiform activity with neurobiological process behind the epilepsy. DEEs manifests during early infantile or childhood period, although adults can be affected too. Genetic variants are recognized to be the etiologies on most patients with DEEs. A cohort study of DEEs that was conducted before (with total patients of 197) showed that almost one third had pathogenic variants in known genes. A greater number of genetics variants are associated with an increased risk of expressing DEEs. Other etiologies and risk factors associated with DEE include.[7]

- Structural: e.g tuberous sclerosis complex (TSC), hypothalamic hamartomas, hemimegalencephaly.[7]
- Metabolic: e.g pyridoxine or biotinidase deficiency, GLUT-1 deficiency.[7]
- Immune disorders: e.g. Rasmussen syndrome.[7]

Patients with DEE, especially in children onset need aggressive treatment.[6]

***Developmental Encephalopathy***

Developmental Encephalopathy (DE) is a term that has separate entity to DEE. The term "developmental encephalopathy" should be used in a condition of a person with developmental delay or intellectual disability, due to a non-progressive brain state who also has co-existing epilepsy. The degree of disability may become more prominent with brain maturation. The risk of epilepsy in this population is higher than the general population but not to the extent that epilepsy itself causes epileptic encephalopathy.[8]

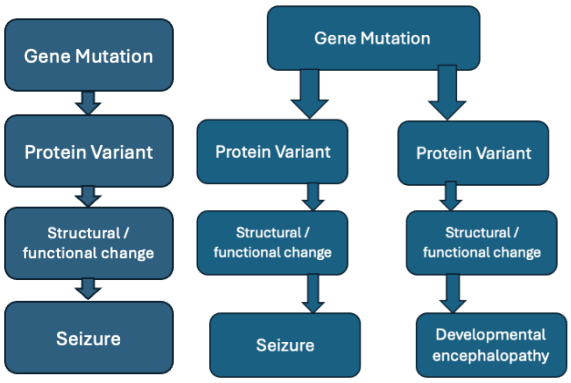


**Figure 1.** Pathological pathways of Developmental encephalopathy [9]

### *Epileptic Encephalopathy*

Epileptic encephalopathy (EE) is a term that refers when epilepsy and/or epileptiform activity affects cognitive and behavioral functions. These conditions can be observed in patients whose preceding level of function was normal or near normal. The unremitting epileptic activity contributes to progressive cerebral dysfunction. The disease course usually is progressive or have waxing-waning course. The underlying etiology varies. Electroencephalographic features and clinical symptoms mirror the specific age-related epileptogenic reaction of immature brain.[9]

Some recognized syndromes for epileptic encephalopathies are Ohtahara syndrome, early myoclonic encephalopathy, West syndrome, Dravet syndrome, Lennox-gastaut syndrome, Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS), and Landau-Kleffner syndrome (LKS). [10]

Early infantile epileptic encephalopathies are a group of disorders comprised of Ohtahara syndrome or early infantile epileptic encephalopathy (EIEE), early myoclonic encephalopathy (EME), and malignant migrating partial seizures in infancy. Ohtahara syndrome is an epilepsy with onset from intrauterine period to 3 months of life. Tonic spasms can be observed and define seizure type that are very frequent and occur in both sleep and wakeful states. Interictal EEG shows burst suppression pattern with no sleep-wake differentiation. Burst can last for 2-6 seconds alternating with periods of suppression lasting for 3-5 seconds. The etiology is heterogenous. Most of the cases are attributable to static structural brain lesions such as focal cortical dysplasia, hemimegaloencephaly, and Aicardi syndrome. [10]

West's syndrome is characterized by epileptic spasms or "salaam attacks", hypsarrhythmia on EEG with developmental delay or regression. Onset is between 3 and 12 months of age. Cluster of sudden, brief, diffuse or fragmented, and tonic contractions of limb muscles are characteristic from epileptic spasm that can be observed from patient with West's syndrome. Symptoms can be accompanied by cry, laughter, or autonomic changes. [10]

Dravet syndrome is described as severe myoclonic epilepsy of infancy (SMEI) with the onset of 5 - 8 months of age. Symptoms would vary from prolonged febrile unilateral-clonic convulsions with alternating patterns in a previously normal child. Seizure is characterized by emergence of multiple seizure types such as myoclonic, atypical absences, and complex focal seizures which frequently progress to status epilepticus and associated with severe psychomotor deterioration. The progression of the symptoms will stop at around 10-12 years of age with decrease in seizure frequency and continue in neurologic sequalae. [10]

**Table 1.** Differentiation in patients with DEE [9]

| | Developmental Encephalopathy (DE) | DEE with dual impact on cognition from developmental | DEE predominantly related to epileptic encephalopathy |
|---|---|---|---|
| **Etiology** | Condition due to underlying static etiology e.g. hypoxic brain insult | Condition due to underlying etiology e.g. TSC, Dravet syndrome, most commonly with gene mutation | Condition due to the impact of the epilepsy e.g. EE-CSWS |
| **Clinical** | May have systemic or focal neurological features, neurocutaneous markers. May be normal. | May have systemic or focal neurological features, neurocutaneous markers. May be normal | May be normal or hypotonic, depending on seizure control |
| **Age at onset** | *In utero* or shortly after birth | Any age, most have onset in infancy or early childhood | Any age but most in childhood |
| **Past medical history** | Often abnormal | Either abnormal or normal | Usually normal |
| **Cognition** | Abnormal | Abnormal - but may be normal and regress, or deteriorate from a low baseline | Regression, improves with seizure control |
| **EEG** | Abnormal in established cases | Abnormal in established cases | Abnormal. Can return to normal if seizures are controlled. Mostly slow with frequent epileptiform discharges |
| **Outcome** | Neurocognition and neurobehavior remain impaired even with seizure control | Neurocognition and neurobehavior remain impaired even with seizure control although some improvement may occur | Neurocognition and neurobehavior may significantly improve with control of seizures and resolution of interictal epileptiform activity. |

Lennox-Gastaut syndrome (LGS) is one of the severe forms of epileptic encephalopathy with the onset of 1-8 years of age (mainly between 2-5 years of age). LGS is characterized by polymorphic seizures including tonic, atypical absence, atonic, and myoclonic seizures. "Drop attacks" can be observed in nearly 50% of children and frequently cause injuries to patients. Nonconvulsive status epilepticus happened in two-thirds of the patients, while twenty percent experienced epileptic spasms. The cognitive stagnation and deterioration are common and fluctuates with the frequency of seizures. [10]

### *Routine Investigations*

Diagnostic investigation has become a very important factor in determining DEEs from other conditions. With collecting clinical history for risk factors, clinical markers, and seizure semiology, other diagnostic investigations have very been helpful in identifying electroclinical syndrome. Electroencephalograms (EEGs) are a diagnostic tool that can be very helpful in distinguishing different syndromes of DEEs. Specific syndromes such as Ohtahara syndrome can be found in EEG as suppression burst, hypsarrhythmia in West syndrome, and continuous slow spike-and-wave typically in 1,5-2,5 Hz during sleep in CSWS. Spike-wave discharge at frequency of <2,5 Hz can be found in Lennox-Gastaut syndrome. [11]

Neuroimaging can be useful in determining structural abnormalities such as malformations of cortical development and hypoxic injuries. The gold standard recommended for investigation of infants and children with epilepsy would be Brain MRI.

Metabolic workup and immune testing can be other investigations. Genetic examination with next generation sequencing (NGS) is suggested. [11]

### *Intervention of Care*

In patients with DE, interventions should include seizures control. However, seizures control does not change the baseline of functioning in patients but can lead to an improvement in quality of life. Decline in seizure control can happen and during these phases, more aggressive seizure management should be considered. Status epilepticus would be an extreme version and should be considered for onset in the setting of an intercurrent respiratory infection. Chronic polypharmacy or high level of ASMs should be avoided since they are more likely to be harmful to a person with DE. [12]

In EE cases, patients develop specific epilepsy-driven encephalopathy. This condition requires aggressive antiseizure interventions as this can lead to significant improvement in cognition and behavior. Suppression of epileptiform abnormalities on the EEG might lead to improvement in cognitive function although usually it won't necessarily return to normal function. [13]

Patients with developmental and epileptic encephalopathies (DEE) require balanced management considering both their cognitive development and seizure control. Treatment aims for improved epilepsy control without over-medication, as uncontrolled seizures can worsen their condition. Despite the challenges, interventions are crucial for safety and quality of life. Targeted treatments, like new medications or gene therapy, show promise in this context. [12,13]

## Conclusion

Developmental and Epileptic Encephalopathies (DEEs) are a subset of epilepsy disorders with early onset and significant developmental impairment, often requiring aggressive treatment. Genetic factors play a key role, alongside various structural, metabolic, and immune-related causes. Early intervention and targeted treatments are crucial for managing DEEs and improving patient outcomes. Further research is needed to better understand the underlying mechanisms and genetic pathways of DEEs.

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