



**VILNIUS UNIVERSITY
FACULTY OF MEDICINE**

Medicine

Neurology and Neurosurgery clinic

Gerli Gloria Gul, 6th year, Group 9

Integrated study master's thesis

Clinical Picture of Childhood-Onset Epilepsy in Adulthood. Literature Review

Supervisor *Neurologist, PhD, Rūta Mameniškienė*

Head of the department or clinic *Professor, MD, PhD, Dalius Jatužis*

Vilnius, 2026

Student's email *gerli.gul@mf.stud.vu.lt*

Acknowledgements

I would like to thank Neurologist, PhD, Rūta Mameniškienė for supervising this thesis.

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1 Objective

The objective of this thesis is to review the literature on selected childhood-onset epilepsy syndromes and describe how their clinical picture, seizures, EEG findings, cognitive function and long-term outcomes evolve into adulthood.

2 Methodology

This Literature review was mainly based on using the PubMed database. Additionally, websites ILAE, AMBOSS, WHO and Epilepsy foundation was used. The search was focusing on developmental and epileptic encephalopathies with concentrating on specific syndromes: Dravet syndrome, West syndrome, Lennox-Gastaut syndrome, Epilepsy with myoclonic-atonic seizures/Doose syndrome and Landau-Kleffner syndrome.

The following keywords were used finding material in PubMed: "Long-term outcome of developmental and epileptic encephalopathies", "Dravet syndrome and EEG", "Dravet syndrome and long-term outcome", "Menkes disease and West syndrome", "West syndrome and EEG: long-term outcome", "Infantile spasms to Lennox-Gastaut", "West syndrome long-term outcome", "Lennox-Gastaut syndrome etiology", "Lennox-Gastaut and EEG", "Epilepsy with myoclonic-atonic seizure", "Doose syndrome clinical characteristic", "Epilepsy with myoclonic-atonic seizures long-term outcome", "Epileptic encephalopathy with continuous spike-waves during slow-wave sleep", "Landau-Kleffner syndrome", "Landau-Kleffner syndrome etiology".

The article which was used as the main source in this review was: "Long-term outcome of developmental and epileptic encephalopathies" as it provided good overview and knowledge of different syndromes and therefore guided the selection of syndrome-specific articles.

Limitations on searching articles was mainly based on to articles published within the last 10 years, to include the most recent evidence. However, in some rare syndromes there was not enough recent publications and therefore, older articles were also included. In these studies, syndrome was well-described, or they focused more on etiology, EEG features or long-term outcome which may have been missing from the latest studies.

Screening of the articles was based on the title and the abstract. Inclusion was according to relevancy to the topic of the thesis and provided information on at least one of the following: definition, etiology, seizures, cognitive function, development, EEG findings, evolution of the syndrome, long-term outcomes. Excluding of the articles was based on if they were not clearly

related to syndromes or they focused only partly to selected syndromes or did not provide enough information for the purposes of this review.

After the search, relevant articles which was found potential for this review, were read in more detail and the final selection was based on significance to the topic and were they focusing on those factors what was needed for this thesis. New review articles and originals studies were both used. In cases were recent studies was not found, older articles were used to provide important background information.

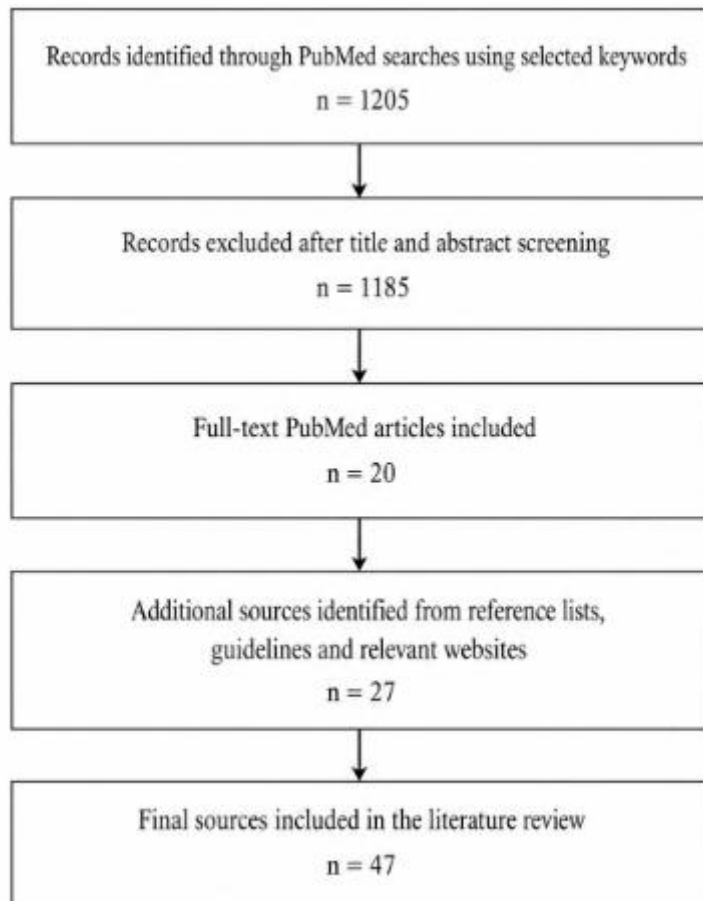


Figure. Flow chart of literature selection process.

The Pubmed searches identified 1205 records using the selected keyword combinations. Titles and abstracts were screened which were relevance to childhood-onset epilepsy, selected epilepsy syndromes, EEG findings, etiology, clinical evolution and long-term outcome. After screening, 1185 records were excluded because they were not directly relevant to the aim of the thesis. 20 full-text PubMed articles were included. In addition, 27 sources were identified from reference lists, clinical guidelines and relevant medical websites. Finally, 47 sources were included in this literature review.

Since this thesis was conducted as a narrative literature review, the selection of sources was based on relevance to the thesis aim rather than a systemic review protocol.

3 Summary

This literature review focused on selected childhood-onset epilepsies and how they evolve over time until adulthood. Among different childhood-onset epilepsies, this writing focused more deeply on Dravet syndrome, West syndrome, Lennox-Gastaut syndrome, Epilepsy with myoclonic-atonic seizures (EMAS) and Landau-Kleffner syndrome. Additionally, few emerging syndrome were briefly introduced: DEE-SWAS, FIRES, EIMFS and SeLFNIE. The purpose of this review was to describe how seizures, EEG findings, cognitive function and clinical features changes with age and which factors seem to be linked to long-term outcome.

Studies which was reviewed showed markedly that childhood-onset epilepsies are very heterogenous. Long-term outcome is depending on several aspects for instance etiology, age at onset, type of syndrome, seizure severity, abnormalities on EEG and response to treatment. In many cases seizure frequency tends to lower with age and some seizure types may disappear, but it is not promising necessarily good overall outcome. Cognitive, behavioral, motor or language difficulties commonly remain into adulthood.

In Dravet syndrome, it is common that seizure pattern changes over time. Prolonged febrile seizures, myoclonic seizures and status epilepticus are typical in childhood, while in adulthood seizures continues in different for and tends to appear during sleep. Additionally, many adults have intellectual disability, gait problems and need support in everyday life. Even if seizures becomes less frequent, the syndrome usually remains severe.

Outcome of West syndrome varies a lot depending on etiology and how quickly treatment is initiated. Early and effective treatment was linked to better developmental outcome especially in children with no underlying structural cause. However, many patients have poor long-term cognitive outcome, persisent seizures, increased mortality or later develops Lennox-Gastaut syndrome.

One of the poorest long-term outcome of syndromes which was reviewed was Lennox-Gastaut syndrome. Seizure types and EEG abnormalities may change with age, however complete seizure remission is uncommon. Many patients continue to have seizures, especially tonic seizures during sleep. Additionally, most have moderate to severe intellectual disability and needs support in everyday life.

Epilepsy with myoclonic-atonic seizures (EMAS) showed widest variation in outcome. Some patients become seizure free and develop normally or near to normal, while the others may have more severe course with drug-resistant seizures, non-convulsive status epilepticus and cognitive difficulties in later life. Poor outcome was linked to early onset, tonic seizures, resistance to treatment, prolonged status epilepticus and persistent EEG abnormalities.

Landau-Kleffner syndrome is different in some aspects comparing to other syndromes. Seizures commonly improve or stop by adolescence and abnormalities on EEG may also lessen, however language difficulties may remain for several years and can have major effect on school, communication and quality of life. In this syndrome the long-term burden often comes more from persistent aphasia than from seizures.

Overall, this review shows that long-term outcome does not only depend on seizures alone. In many syndromes, outcome is depending also by underlying etiology and by the effect of epileptic activity on the developing brain.

4 Santrauka (Summary in Lithuanian)

Šioje literatūros apžvalgoje nagrinėta vaikystėje prasidedančių epilepsijų eiga iki suaugusiojo amžiaus. Aptarti pagrindiniai sindromai: Dravet, West, Lennox-Gastaut, epilepsija su miokloniniais-atoniniais priepuoliais (EMAS) ir Landau-Kleffner sindromas, taip pat trumpai naujesni sindromai: DEE-SWAS, FIRES, EIMFS ir SeLFNIE. Analizuota, kaip su amžiumi kinta priepuoliai, EEG radiniai, kognityvinės funkcijos ir klinikiniai požymiai bei kokie veiksniai lemia ilgalaikę baigtį.

Literatūros duomenys rodo, kad vaikystėje prasidedančios epilepsijos yra heterogeniškos, o ilgalaikė baigtis priklauso nuo etiologijos, ligos pradžios amžiaus, sindromo tipo, priepuolių sunkumo, EEG pakitimų ir atsako į gydymą. Nors daugeliu atvejų priepuoliai su amžiumi retėja, kognityviniai, elgesio, motorikos ar kalbos sutrikimai dažnai išlieka ir suaugus.

Dravet sindromui būdinga kintanti priepuolių eiga – vaikystėje vyrauja febriliniai ir miokloniniai priepuoliai bei epilepsinė būklė, o suaugus dažnesni priepuoliai miego metu. Daugeliui pacientų išlieka intelekto negalia, eisenos sutrikimai ir kasdienės pagalbos poreikis.

West sindromo baigtis glaudžiai susijusi su etiologija ir ankstyvu gydymu, tačiau daliai pacientų išlieka kognityviniai sutrikimai ar išsivysto Lennox–Gastaut sindromas. Pastarajam būdinga viena sunkiausių ilgalaikių baigčių – nuolatiniai priepuoliai, dažnai toniniai miego metu, ir vidutinė ar sunki intelekto negalia.

Epilepsija su miokloniniais-atoniniais priepuoliais (EMAS) pasižymi itin įvairia prognoze – nuo visiškos remisijos iki vaistams atsparios epilepsijos su kognityviniais sunkumais. Blogesnė baigtis siejama su ankstyva ligos pradžia, toniniais priepuoliais, epilepsine būkle ir išliekančiais EEG pakitimais. Landau–Kleffner sindrome priepuoliai dažnai suretėja paauglystėje, tačiau ilgalaikę ligos naštą dažniausiai lemia išliekanti afazija ir kalbos sutrikimai. Apžvalga pabrėžia, kad ilgalaikę vaikystėje prasidedančių epilepsijų baigtį lemia ne tik priepuolių kontrolė, bet ir pagrindinė etiologija bei epilepsinio aktyvumo poveikis besivystančioms smegenims.

5 An overview of epilepsy

5.1 Definition of epilepsy

Epilepsy is generally defined as brain disease accompanied with recurrent unprovoked seizures [1]. Where as epileptic seizure is defined according International League Against Epilepsy: "A transient occurrence of signs and/or symptoms due the abnormal excessive or synchronous neuronal activity in the brain.". International League Against Epilepsy has set clinical criterias for diagnosing epilepsy if a person has: "1.) At least two unprovoked seizures or reflex seizures separated more than 24h apart, 2.) One unprovoked seizure or reflex seizure with high risk of recurrence (risk more than 60% over the next 10 years), or 3.) Epilepsy syndrome." Risk for recurrent seizure could be evaluated by EEG or brain imaging, where we could see epileptiform activity or epileptogenic abnormality. The individual is seen to be "cured" when, an individual is older than certain epilepsy age dependent syndrome, or an individual has not had seizures more than 10 years and have not been using antiepileptic medications more than 5 years anymore. [1]

5.2 Classification of epilepsy

After the diagnosis of epilepsy has been established, classification is carried out in three different level: seizure type, epilepsy type and epilepsy syndrome [2]. Brain imaging, EEG and other investigations are used as confirmation of classifications in all three levels. Whenever possible, classification should be made in all mentioned levels. Etiology also should be considered from the beginning and reasses throughout diagnostic process, as identifying the cause can improve classification and can lead to the right treatment. Epilepsies are classified as generalized epilepsy, focal epilepsy, combined generalized and focal epilepsy and epilepsy of unknown.

5.2.1 Generalized epilepsy

Generalized epilepsy is characterized by generalized seizure types and may show distinct EEG abnormalities interictally or ictally for instance generalized spike-wave activity [2]. Genetic generalized epilepsy is a form of generalized epilepsy in which the etiology is genetic. The Genetic cause may arise from a de novo pathogenic variant, be inherited within a family or result from complex polygenic inheritance. Idiopathic generalized epilepsy is a subgroup of genetic generalized epilepsy and includes four epilepsy syndromes: childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy and epilepsy with generalized tonic-clonic seizures alone. These syndromes result from polygenic inheritance with or without the influence of environmental factors. Seizure types which are seen in these syndromes may include absence seizures, myoclonic seizures, generalized tonic-clonic seizures or a combination of these.

5.2.2 Focal epilepsy

Focal epilepsy includes focal seizure types and may have typical interictal or ictal EEG activity, such as focal sharp waves or focal slowing [2]. Brain imaging is useful tool for supporting the diagnosis when it shows focal structural lesion. However, focal epilepsy can occur in patients with normal brain imaging for instance when the cause is genetic. Focal epilepsy may be unifocal, multifocal or hemispheric.

Self-limited focal epilepsies of childhood (SeLFE) are a group of epilepsy syndromes and it includes the following syndromes: self-limited epilepsy with autonomic seizures, self-limited epilepsy with centrotemporal spikes, childhood occipital visual epilepsy and photosensitive occipital lobe epilepsy. These syndrome make up 25% of all epilepsy cases with onset in childhood. SeLFE syndromes have several common features: focal seizures occur in age-dependent manner, brain imaging is normal, cognition and neurological examination are often normal, remission occurs by puberty, seizures often respond well to treatment and each syndrome has its own characteristic clinical and EEG findings.

5.2.3 Combined generalized and focal epilepsy

Some individuals may experience both generalized and focal seizure types and EEG may show abnormalities associated with both groups [2]. This pattern may be seen in syndromes such as Dravet syndrome and Lennox-Gastaut syndrome which are classified in combined generalized and focal epilepsies.

5.2.4 Unknown epilepsy

This group is used when an individual has epilepsy but there is not enough information to determine whether it is focal, generalized or combined [2]. It may happen when available data are limited, for instance if EEG is normal or uninformative.

5.3 Classification of epileptic seizures:

ILAE has updated the classification of epileptic seizures in 2025 which aim was to simplify seizure terminology, reduces the number of seizure types and improve the clinical and international description of seizures [3]. The new classification includes classifiers and descriptors. Classifiers identify the fundamental biological seizure type and are important for diagnosis, treatment and prognosis. Descriptors provide additional information about the clinical manifestations and evolution of seizures. Epileptic seizures are divided into four classes: focal seizures, generalized seizures, unknown seizures whether focal or generalized and unclassified seizures.

5.3.1 Focal seizures

Focal seizures originate from networks that are limited to one hemisphere [3]. The site of onset is typically consistent, however it may spread to the opposite hemisphere. In focal to bilateral tonic-clonic seizures, epileptic discharges start focally and spread to both hemispheres, leading to impaired or loss of consciousness and followed by bilateral tonic muscle activation and a clonic phase with gradually decreasing jerks. Focal seizures are further classified according to whether consciousness is preserved or impaired. Consciousness is evaluated according to awareness (the patient's ability to remember the events) and responsiveness (the patient's ability to give an appropriate response during the seizure). Focal seizures may also be described using descriptors, according to observable clinical features, for instance motor, sensory, cognitive, autonomic, emotional and other manifestations.

5.3.2 Generalized seizures

Generalized seizures originate in and rapidly engage bilaterally distributed networks [3]. Seizure types included in this category are tonic-clonic, tonic, clonic, myoclonic, atonic, absence and epileptic spasms. The new ILAE 2025 classification focuses more on observable and non-observable manifestations and the chronological sequence of symptoms instead of the earlier classification into motor and non-motor seizures.

5.3.3 Unknown whether focal or generalized seizures

This category is used when there is not enough information to determine whether the seizure is focal or generalized [3]. For instance, this may occur when the event is unwitnessed or when the clinical information and EEG findings remain incomplete.

5.3.4 Unclassified seizures

Is defined as when seizure is clearly epileptic but there is not enough information for further classification [3].

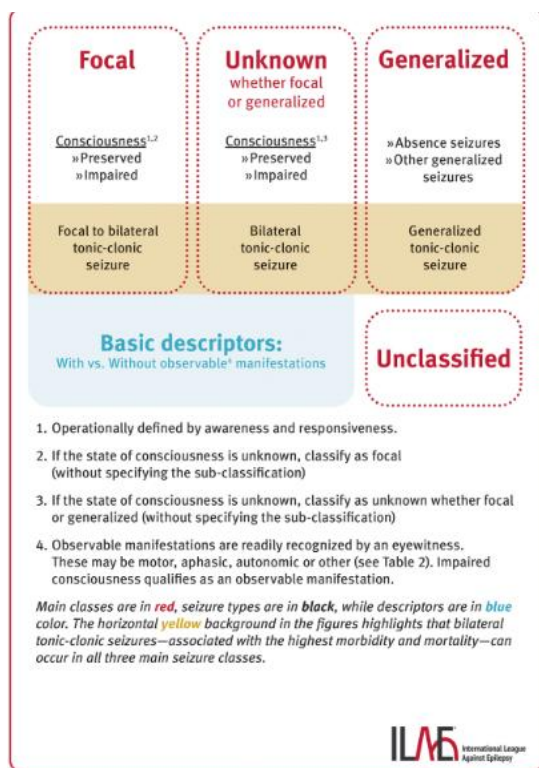


Figure 1. Basic version of the seizure classification [3]

5.4 Epilepsy syndrome

Epilepsy syndrome is defined as a specific combination of clinical and EEG features and commonly supported by etiological factors for instance structural, genetic, metabolic, immune or infectious causes [4]. For prognosis and treatment, it is important to distinguish syndrome in a person with epilepsy. These syndromes are commonly age-related and are associated with particular comorbidities.

Epilepsy syndromes are classified into four categories based on the age of onset: 1.) neonatal and infantile onset, 2.) Childhood onset, 3.) Variable age at onset (if it could occur in both pediatric patients <18 years and adults >19 years) and 4.) idiopathic generalized epilepsies [4]. These can further to be divided into generalized epilepsy syndrome, focal epilepsy syndrome, combined generalized and focal epilepsy syndrome and developmental and epileptic encephalopathies.

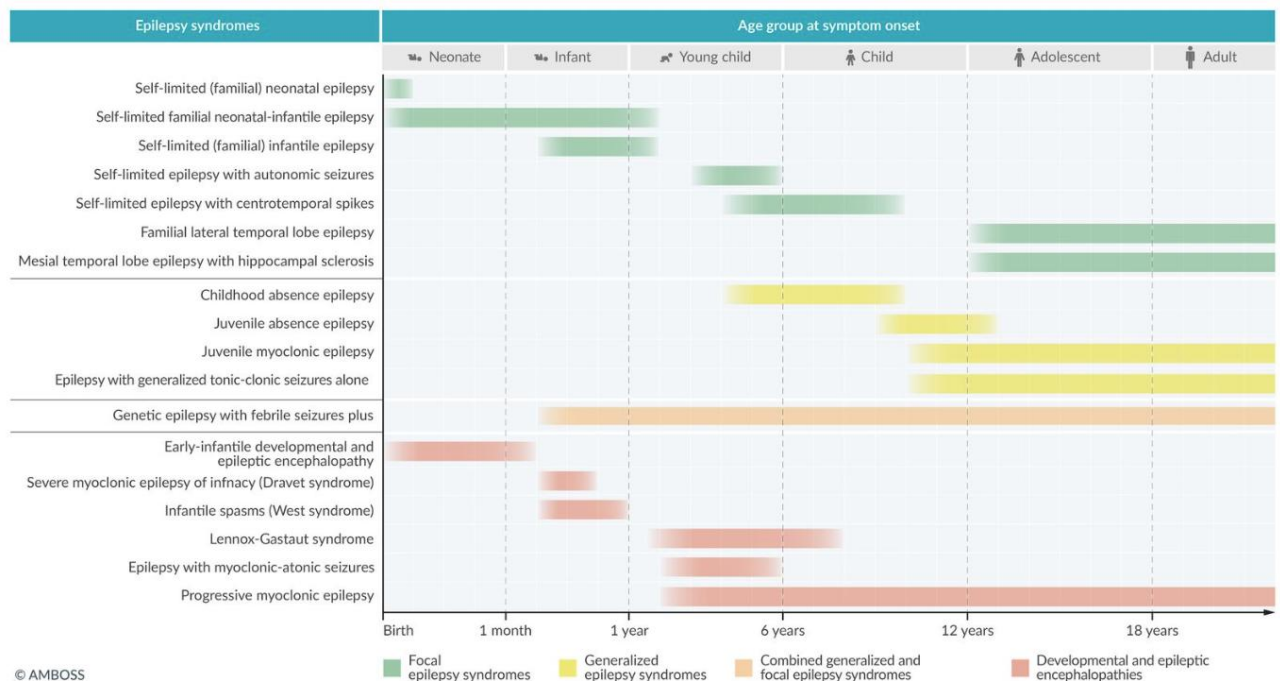


Figure 2. Overview of key epilepsy syndromes with typical age of onset [5]

5.5 Epidemiology

Epilepsy is the most common neurological disease worldwide [6]. The lifetime prevalence of epilepsy is approximately 7.6 per 1,000 individuals. It affects people of all ages, but its incidence demonstrates two prominent peaks: one in early childhood and another in the elderly population. A higher incidence of epilepsy is seen in low- and middle-income countries 139 per 100 000 individuals annually compared to high-income countries.

5.6 Etiology

Assessment of the seizure etiology is crucial as it plays an important role in treatment and prognosis [7]. The International League Against Epilepsy has identified six categories of epilepsy etiology: structural, genetic, infectious, metabolic, immune and unknown. An Individual could be categorized into more than one etiological category and no etiology category takes priority over to another,

although it is important to prioritize the most relevant category based on the individual clinical situation. Person with tuberous sclerosis complex falls into both the structural and a genetic etiology categories. The structural etiology is important when considering epilepsy surgery, while the genetic cause is important for genetic counseling and targeted therapy for instance mTOR inhibitors.

5.6.1 Structural etiology

Structural etiology refers to a neuroimaging finding that can be the cause of seizures, which should also be supported by corresponding EEG and clinical evidence [7]. MRI is a commonly used neuroimaging modality in epilepsy and can reveal fine structural abnormalities using dedicated epilepsy protocols.

Causes of structural abnormalities can be classified as acquired, genetic or a combination of both. Commonly known acquired causes include hypoxic-ischemic encephalopathy, traumatic brain injury, infections and stroke. A prominent genetic cause is tuberous sclerosis complex, which is caused by gene mutations in TSC1 and TSC2 and leads to structural abnormalities.

Certain lesions may have either a genetic or an acquired origin, for example polymicrogyria. Polymicrogyria is characterized by an excessive number of abnormally small brain folds [8]. Polymicrogyria may be caused either by a genetic mutation of GPR56 or may be acquired due to intrauterine cytomegalovirus infection [7]. It is important to note that if a neuroimaging abnormality does not align with the seizure types or EEG results, the probability that this abnormality is causing the patient's epilepsy is unlikely.

5.6.2 Genetic etiology

Epilepsy of genetic etiology results from specific gene mutations or copy number variations that predispose individuals to seizures [7]. Genetic epilepsies exhibit marked variability and in many cases diagnosis is based on the presumption of a genetic cause even though the exact gene has not yet been identified. For instance Benign Familial Neonatal Epilepsy is certainly genetic as it follows an autosomal dominant pattern and researches have identified specific mutations in the KCNQ2 or KCNQ3 genes. However, Autosomal Dominant Nocturnal Frontal Lobe Epilepsy has a clear autosomal dominant inheritance pattern, but a specific gene mutation has been identified in only a small number of patients. In most affected individuals, the exact genetic cause is still unknown.

Dravet syndrome is a well-known genetic epilepsy. In over 80% of patients, it is caused by a mutation in the SCN1A gene. However, this gene mutation can cause a milder epilepsy type called

Genetic Epilepsy with Febrile Seizures Plus. Knowing the gene involved can help guide treatment, but it is not enough to predict how severe the epilepsy will be, therefore adding EEG findings and clinical features is crucial.

Genetic epilepsy does not necessarily mean that it is inherited. Many genetic mutations associated with epilepsy arise de novo and are therefore not passed on from parents. In infants with severe developmental and epileptic encephalopathies, approximately 30-50% of identified gene mutations are de novo. Although there is a 50% of risk for offspring to inherit de novo mutation, this does not mean that offspring will have epilepsy, as clinical expression depends on the penetrance of the mutation.

Eventhough genetic epilepsy has a genetic basis, environmental factors may play a important role. For example, some individuals with epilepsy are triggered by environmental factors such as sleep deprivation or stress precipitate seizures. However, genetic etiology refers a mutation which has significant impact on the individual epilepsy [7].

5.6.3 Infectious etiology

Infections represent the leading cause of epilepsy worldwide [7]. Infectious etiology refers to epilepsy that develops as a result of a previous or ongoing known infection where the seizures are main symptom of the disorder. It is important to exclude acute infections for example meningitis or encephalitis, since they could provoke seizures, but do not meet the definition of epilepsy.

Examples of infections that may cause epilepsy are neurocysticercosis, tuberculosis, HIV, and congenital cytomegalovirus. Some of these could be classified under structural etiology, but when considering treatment options it is often more relevant to classify them as having an infectious origin.

5.6.4 Metabolic etiology

Metabolic etiology applies to individuals with an underlying metabolic disorder whose main symptom is seizures [7]. As in infectious etiology, it is important to distinguish temporary metabolic imbalance which could provoke seizures, but does not meet the definition of epilepsy as in acute infections. Examples of metabolic disorders are porphyria, uremia, aminoacidopathies and pyridoxine-dependent seizures. Genetic origin plays an important role in many metabolic epilepsies, although some may be acquired as in cerebral folate deficiency. It is crucial to identify metabolic causes as this guides appropriate therapy and may help prevent cognitive impairment.

5.6.5 Immune etiology

Immune epilepsy refers to seizures that occur as the main symptom of an underlying immune disorder [7]. In an immune disorder, the immune system causes inflammation of the brain. Recently, several types of immune-related epilepsies have been recognized in both children and adults. These conditions are being diagnosed more frequently now due to better antibody testing. Examples include anti-NMDA receptor encephalitis and anti-LGI1 encephalitis. Because these epilepsies respond to targeted immunotherapy, they are considered a distinct category.

5.6.6 Unknown etiology

Unknown etiology refers to patients in whom the cause of epilepsy cannot be defined [7]. It is important to recognize that identifying the cause of epilepsy depends on the available diagnostic tools and current knowledge in a specific area.

6 Introduction to the developmental and epileptic encephalopathies (DEE)

6.1 Epileptic encephalopathy (EE)

Epileptic encephalopathies refer to conditions where the brain function is directly damaged by seizures and abnormal electrical activity in the brain [9]. They negatively affect cognitive function and causes behavioral impairments. These impairments are worse than what would be expected from the underlying brain disorder alone. The conditions are characterized by frequent abnormal EEG activity and seizures, which slow development and can even cause loss of previously learned skills.

It should be noted that, in the classic encephalopathy of Landau-Kleffner syndrome, approximately 30% of affected individuals never develop clinical seizures [10]. However, their sleep EEG shows continuous spike-wave activity during sleep and additionally 85% of non-REM sleep is occupied by bilateral spike-wave discharges. In Landau-Kleffner syndrome, children experience significant developmental regression with behavioral difficulties. A Common feature is auditory agnosia, meaning that they are unable to recognize or understand everyday sounds for example a doorbell.

Overall EE is not dependent on whether the child has had normal or abnormal development before the epilepsy began [11]. The main goal of treating an epileptic encephalopathy is to diminish abnormal epileptiform activity and therefore normal development can resume or even progress [10]. The benefit depends on additional factors such as the patient's age, associated comorbidities, other medications being used and most relevant the underlying cause of the disorder.

Even though the ILAE introduced a revised classification in 2017, changing "Epileptic encephalopathy" to "Developmental and epileptic encephalopathy", it is important to recognize these conditions where seizures and EEG abnormalities are the main reasons causing brain dysfunction.

6.2 Developmental encephalopathy (DE)

Developmental encephalopathy is defined as a condition in which individual has developmental delay or cognitive disability due to a non-progressive brain condition and who also has epilepsy [11]. In these individuals the risk of having epilepsy is higher than average, however the epilepsy does not worsen their developmental impairment. The extent of developmental disability may become more noticeable as the brain matures. One example would be an infant who has suffered on hypoxia during birth, which has caused non-progressive brain damage. This infant may have developed developmental impairment and occasional seizures. Even with aggressive treatment for seizures it does not significantly improve the infant's baseline function and developmental abilities remain mostly unchanged.

6.3 Developmental and epileptic encephalopathy (DEE)

As mentioned previously, former epileptic encephalopathies are now considered as developmental and epileptic encephalopathies [10]. The reason behind this change in classification is that research showed that many genes that cause the epileptic encephalopathies also directly and independently impact development.

Developmental and epileptic encephalopathy is defined a condition in which an individual already has cognitive and behavioral impairment before the onset of epilepsy [11]. The epilepsy involves frequent seizures and EEG abnormalities which contributes even more cognitive and behavioral impairments. The etiology is commonly genetic, where the genetic variant causes intellectual impairment and severe epilepsy at the same time. Controlling the seizures does not usually improve the cognitive or developmental impairments.

According to Scheffer and Liao's 2020 review, the following syndromes are key examples of developmental and epileptic encephalopathies: Ohtahara syndrome, early myoclonic epilepsy, epilepsy of infantile onset with migrating focal seizures, West syndrome, Dravet syndrome, myoclonic-atonic epilepsy, Lennox-Gastaut syndrome, focal lesional epilepsies for example tuberous sclerosis, hemimegalencephaly, hypothalamic hamartoma, Rasmussen syndrome, and the epilepsy-aphasia spectrum for example Landau-Kleffner syndrome and continuous spike and wave in sleep (CSWS) [10].

6.4 An Overview of the main DEE -syndromes

6.4.1 Dravet syndrome

From developmental and epileptic encephalopathies, Dravet syndrome is one of the most well-studied forms [11]. Charlotte Dravet first described in 1978 a group of children with early-onset epilepsy that was highly resistant to treatment [12]. Affected individuals experienced many seizure types, although myoclonic seizures were a prominent type. In addition, individuals developed moderate to severe intellectual disability. This condition was distinguished from Lennox-Gastaut syndrome by using the term severe myoclonic epilepsy of infancy. Quite soon, research groups recognized similar clinical features and the disorder was named as Dravet syndrome.

In 2001, genetic factors were identified as a primary cause for this disorder. Approximately 85% of affected individuals with this syndrome, were found to carry pathogenic variants in the SCN1A gene. This discovery represented one of the earliest major breakthroughs in epilepsy genetics. It confirmed a direct link between a well-defined electroclinical epilepsy syndrome and a de novo genetic mutation.

Individuals with Dravet syndrome experience different types of comorbidities [12]. The majority develop moderate to severe intellectual impairments, disturbances in motor function, behaviour and sleep are also common. There is still debate how SCN1A mutation and/or seizure frequency affect the severity of these comorbidities. Moreover, there is a significant risk of sudden unexpected death in epilepsy when compared with other childhood epilepsy syndromes. However, in recent years, several new antiseizure medications have become available. In addition, new gene-based therapies are expected to emerge soon.

6.4.2 West syndrome

In 1841, the condition was first described by the physician William James West [13]. He observed the disorder in his own son, whose seizures began at 4 months of age and also had developmental delay. The seizures occurred in clusters of up to 20 spasms within 3 minutes, recurring several times a day. West also noticed generally poor prognosis in similar cases.

In 1951, physicians Hector J. Vazques and Marcos Turner described a group of children with similar flexor spasms, intellectual disability and abnormal EEG findings [13]. In 1952, Frederic and Lorna Gibbs introduced the term hypsarrhythmia to describe an EEG pattern characterized by with high-voltage, chaotic and slow waves and spikes in cortical areas of the brain. However, it was later discovered that hypsarrhythmia is absent in approximately 50% of children with infantile spasms. In 1960, neurologist Henri Gastaut proposed naming the condition West syndrome.

However, research has shown since 1990 that West syndrome is not a single disease, instead it may result from several causes such as structural abnormalities, genetic and metabolic disturbances affecting brain development some of which may be treated with epilepsy surgery [13]. Therefore, it is understandable that the International League Against Epilepsy proposed new classification of epilepsy syndromes with onset in neonates and infants in 2022. Currently, there is a broader term called infantile epileptic spasms syndromes (IESS) which encompasses children who have clinical features of West syndrome even if hypsarrhythmia is not seen on EEG, or when EEG is not obtainable.

6.4.3 Doose syndrome/Myoclonic-Atonic Epilepsy

In 1922, Hunt described the first atonic seizures [14]. When atonic seizures occurred together with absence or myoclonic seizures they were classified collectively under the name of petit mal. Therefore, for several years, children who presented with different combinations of atonic, myoclonic and absence seizures were grouped under the same diagnosis. This classification continued until Lennox-Gastaut syndrome was recognized. In the 1960s, researchers noticed that myoclonic seizures could occur separately from Lennox-Gastaut syndrome. In 1968, Krause reported myoclonic and atonic seizures, however it is likely that many epilepsy syndromes for example, LGS and myoclonic absence seizures were grouped as the same entity.

In 1970, Dr Hermann Doose defined myoclonic-astatic epilepsy (MAE) as a separate epilepsy syndrome [14]. Doose described children who shared a characteristic seizure types combined with typical EEG findings and clinical features. Shortly after that, International League Against Epilepsy formally recognized myoclonic-astatic epilepsy as being one form of symptomatic generalized

epilepsy and proposed diagnostic criteria for this condition. ILAE renamed the condition as epilepsy with myoclonic-atonic seizures in 2010 and it has persisted until today.

6.4.4 Lennox-Gastaut Syndrome

Lennox-Gastaut syndrome is one of the most severe epileptic encephalopathies of childhood and it was gradually characterized by different researches [15]. In 1938-1939, Frederic Gibbs, Erna Gibbs and William G. Lennox noticed a new EEG pattern which was characterized by slow spike-and-wave discharges at 2 Hz. This pattern was named "petit mal variant", in contrast to typical less severe "petit mal" which had already been distinguished three years earlier and was characterized by absence seizures and 3 Hz spike-and-wave discharges. In addition, they noticed that, unlike 3 Hz spike-and-wave, it was not provoked by hyperventilation, hypoglycemia or hypoxia, but often disappeared with attention or eye opening.

In 1940s-1960s, William G. Lennox recognized that children with this EEG pattern shared a distinct clinical profile [15]. Lennox described a form of epilepsy as a triad: diffuse slow spike-and-wave on EEG, intellectual impairment, multiple seizure types as myoclonic jerks and a variant of absence seizures. Soon after Lennox was deceased, Henri Gastaut organized three symposia about epilepsy syndrome which was proposed by Lennox previously. After examining many patient cases, this syndrome had strong clinical validation and it was not thought to be just a theory anymore. The name was changed to Lennox syndrome as the "petit mal variant" describes only the EEG pattern whereas Lennox had correctly identified the condition as a distinct clinical syndrome. Later, Lennox's daughter, proposed that the syndrome be called Lennox-Gastaut syndrome as honoring her father's original description and Gastaut for confirmation of this syndrome.

6.4.5 Landau-Kleffner syndrome

In the 1950s William M. Landau and Frank R. Kleffner released an article with different cases which described children who developed an acquired aphasia after previously normal language development, together with features of epilepsy [16]. They noticed that loss of language was not due to of a hearing impairment or a progressive neurological disorder, instead there was signs of abnormal epileptiform activity on EEG with or without clinical seizures.

In the 1990s, even though Landau-Kleffner syndrome was having clear diagnostic pattern including language regression and epileptiform activity on EEG, there was still often misdiagnosis [17]. This syndrome was often mixed with speech delay and hearing impairment, because not in all cases the

seizures are present. It was noticed that only 70% of children with LKS was actually having clinical seizures but in all children had abnormal EEG findings.

Long-term follow-up studies of individuals with Landau-Kleffner syndrome showed that seizures and EEG abnormality often improved with age, however language outcomes were variable and less predictable [18]. Even though, some individuals had improvement in language abilities, still persistent and often severe language impairment was more common. Notably, limitations of quality of life were frequently affected due to persistent language difficulties rather than ongoing seizures.

7 Phenotypic changes with growth

As mentioned previously, developmental and epileptic encephalopathy is defined as developmental impairment which is related to the underlying etiology, together epileptiform activity that also causes epileptic encephalopathy [19]. These conditions often have several possible etiologies. Because of this, long-term prognosis depends on the etiology, and factors which are related to epilepsy such as the age at epilepsy onset, seizure types, pattern of EEG abnormalities and epilepsy syndrome duration.

7.1 Dravet syndrome

7.1.1 Definition

Definition of Dravet syndrome is based on the clinical picture [19]. Seizure onset is usually between 5-8 months of age and these infants have so far developed normally [20]. Clinically, seizures are presenting as febrile and afebrile, prolonged unilateral clonic and generalized tonic-clonic seizures [19]. As the syndrome evolves, seizures are accompanied with myoclonic or atypical absence seizures. In the first years, individuals are commonly experiencing prolonged seizures which is often triggered by fever, and additionally leading to hospital admissions [21]. Typically, seizures are resistant to antiseizure medications and from the second year of life children begin to show cognitive and behavioral abnormalities [19].

7.1.2 Etiology

Approximately 80% of individuals with Dravet syndrome are identified with de novo loss-of-function pathogenic variant in the SCN1A gene [19]. In the remaining 20% of cases, other pathogenic variants may be identified or no clear causative variant may be found. Due to the high

frequency of SCN1A pathogenic variants in this syndrome, many authors include this variant in the definition of Dravet syndrome. This genetic testing have been showing several different phenotypes for instance seizure onset may occur as late as 19 months, only 50% of patients with first seizure was febrile seizure, and only 7% of individuals never experience status epilepticus. However, another cohort study showed that 86% of 14 patients with an SCN1A pathogenic variant, developed treatment-resistant seizures[22]. Although an SCN1A pathogenic variant is common in Dravet syndrome, it is not alone sufficient to diagnose this syndrome, because the same variant is seen in other epileptic syndromes for instance in self-limiting syndromes such as genetic epilepsy with febrile seizure plus[19].

7.1.3 EEG

In Dravet syndrome, EEG is typically normal at seizure onset [23]. However, already after one year of age, 90% of patients is having EEG abnormalities [24]. Types of changes and onset on EEG varies among individuals. As the syndrome evolves, generalized, focal or multifocal abnormalities with spikes, spike-waves or polyspike-waves begin to appear on EEG [23]. Over time, individuals are more likely to show focal epileptiform activity and diffuse background slowing [24].

Generalized epileptiform activity tends to remain stable over time.

Studies have shown that in adulthood EEG phenotypes evolves to sawtooth type of pattern at approximately 5-6Hz, which is especially activated by eye closure and during NREM sleep [23]. As mentioned before, EEG abnormalities can be enhanced by eye closing and also by photic stimuli. Photosensitivity is common and it appears in early stages, however it sometimes may be detected only with patterned geometrical visual stimulation. Over time, photosensitivity typically tends to disappear before approximately 20 years of age.

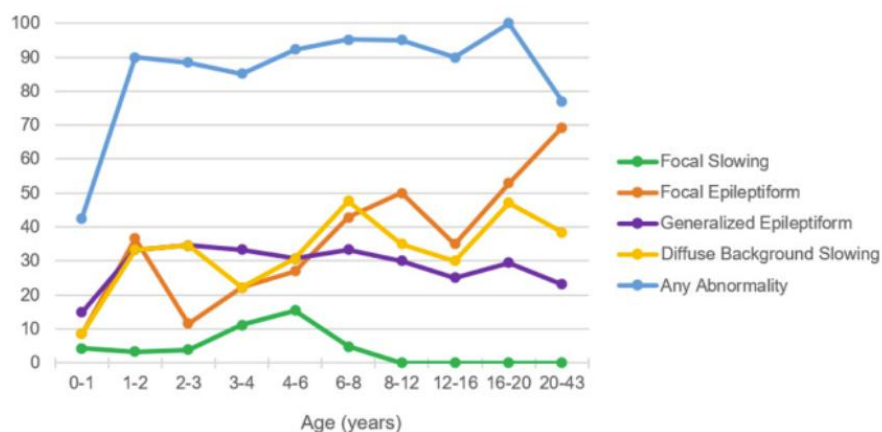


Figure 3. Different EEG abnormalities in patients with Dravet syndrome in different ages [24]

7.1.4 Seizures

Overall, Dravet syndrome evolves in different ways from childhood to adulthood [21]. Seizure frequency often diminishes and some individuals become totally seizure free. Commonly, myoclonic seizures, atypical absences and drop attacks lessen and may be resolved in adulthood. Adults may have fever induced seizures but sensitivity for fever decreases. Retrospective reports have shown that in adulthood seizures tend to appear more often in sleep than previously. Additionally, status epilepticus less commonly requires hospital admission in adulthood. However, cognitive outcomes are commonly poor in adulthood, as they usually present as moderate to severe intellectual disability. Hence, most of adults are dependent on others for daily support and only a few are able to independent living [25].

7.1.5 Long-term outcome

Developmental delay occurs in all patients with Dravet syndrome and it is therefore considered part of the definition of this syndrome [19]. Development usually begins to slow down at approximately 24 months of age but it can appear also earlier or even later, after 4 years of age. Cognitive impairment, personality changes and gait disturbances are followed after developmental delay [21].

A Publication on a large cohort study of patients with SCN1A mutations, reported that approximately 85% of patients suffered severe disability after 15 years of age, and the rest of the patients suffered moderate learning difficulties [19]. Predictors of severe developmental outcome included motor disorder, abnormal EEG at one year of age, status epilepticus and early focal seizures with impairment of awareness. The findings of this study indicated that developmental outcome is partly connected to epileptic features and that the use of antiepileptic medications could improve outcomes.

However, in Dravet syndrome after reaching a plateau phase, where developmental impairment is not further declining, children are not able to achieve expected developmental level proper for their age. There is two theories which could explain the developmental slowing, one is that epilepsy does not affect as much as thought and therefore syndrome is more of a developmental encephalopathy rather than epileptic encephalopathy. Another suggestion is that current antiepileptic medications are not efficient enough for treating epilepsy.

A follow-up study consisting 64 patients with Dravet syndrome into adulthood indicated that this syndrome is a life-long, treatment-resistant epilepsy. Even though, status epilepticus and unilateral

seizures were not detected anymore in adults, yet only five of these individuals were actually seizure free. However, long-term studies of using antiepileptic medication called flenfluramine showed improvement in functional capacity in everyday activities, underlying that that new medications should be developed to improve outcomes for these patients. Long-term management should also focus on the elevated risk of sudden unexplained death in epilepsy. It is noticed that in Dravet syndrome, sudden unexplained death is approximately 9.32 per 1000 person-years, which is higher compared with individuals with other types of refractory epilepsy.

Motor impairments are also common in Dravet syndrome. Many individuals suffer from ataxia, dysarthria, tremor and eye movement disorders [25]. Additionally, gait may develop features resembling as Parkinson's disease, for instance a crouched posture due to flexed knees, kyphosis, dystonia and small steps [21]. These symptoms tend to worsen with age, even with physiotherapy [25]. These motor disturbances may resolve with antiepileptic drug for instance using levodopa [21].

7.2 West syndrome

7.2.1 Definition

West syndrome is commonly described as a triad that includes epileptic spasm, hypsarrhythmia on EEG, and developmental delay, typically with onset between 3 and 12 months of age [19]. Clusters of epileptic spasms are characteristic of this syndrome; however, other seizure types can occur before spasms arises. Not all individuals have the classical West syndrome triad, as developmental slowing may be absent at spasm onset and EEG does not necessarily meet all criteria for classic hypsarrhythmia. For this reason, it is proposed a broader term called "infantile spasm syndrome" for all epilepsy types with infants who has epileptic spasms. Late-onset spasms arise after one year of age and these are considered as a transitional syndrome between West syndrome and Lennox-Gastaut syndrome.

7.2.2 Etiology

Etiology of West syndrome is classified into structural, genetic, metabolic and unknown origin [19]. The structural etiology includes early acquired cerebral lesions which arises prenatally, perinatally or postnatally and are caused by ischemia, infection, trauma, neoplasia or malformations of cerebral cortical development. Key etiologies in this includes subgroup tuberous sclerosis complex (TSC) and type 2 focal cortical dysplasia (FCD II).

West syndrome is not commonly caused by metabolic disorders. However, for instance Menkes disease which is characterized by copper deficiency, commonly leads to West syndrome [26]. Additionally, phenylketonuria has been noticed to be associated to West syndrome, however the exact connection is not yet known [27].

Genetic etiology is the most common group [19]. Psychomotor delay is frequent and it is already present before spasm onset. This group includes chromosomal changes which are often suspected when dysmorphic features are present.

Unknown etiology is usually a mixed type. Some individuals have normal development before spasm onset. This cryptogenic group accounts for approximately 20% of West syndrome cases. It is important that these patients are distinguished from etiology of unknown cases with pre-existing developmental delay, because outcome may be different.

7.2.3 EEG

EEG is characterised by a pattern called hypsarrhythmia [28]. It refers to a disorganized, chaotic background made up high voltage slow delta activity at 1-3Hz waves with spikes or sharp waves from multiple foci. There may be variations, but their clinical importance is the same as in classical hypsarrhythmia. EEG is important to be recorded during sleep, as hypsarrhythmia is not commonly seen in the awake state. Although not every child meets the criteria for classical hypsarrhythmia on EEG, if a child has a normal EEG during both in awake and sleep, infantile spasms are unlikely.

Early recognition of West syndrome and proper initiation of effective treatment can also be reflected in the EEG, and one of the key treatment goals, together with cessation of spasms, is the resolution of hypsarrhythmia. However, if treatment is not sufficient enough, West syndrome may evolve into Lennox-Gastaut syndrome and EEG show paroxysmal fast activity and slow spike-and-wave <2,5Hz [31].

7.2.4 Seizures

Infantile spasms are typically characterized by flexion jerks, also called salaam attacks, with sudden, brief clusters of muscle spasms, which most often are provoked by awakening [28]. Spasms can be asymmetrical and may involve extension movements rather than typical flexion pattern. Additionally, spasms may be difficult to notice, as they can manifest as repetitive yawning, small eye or chin movements.

7.2.5 Long-term outcome

West syndrome is often associated with poor neurocognitive outcomes and early mortality in approximately 33% of patients, and a higher risk for this syndrome to evolve to another syndrome, for example Lennox-Gastaut syndrome [30].

However, there are two factors that are linked to a good long-term prognosis: sufficient treatment with rapid control of spasms and cryptogenic etiology [19]. Among individuals with cryptogenic etiology, as much as 80% may have normal neurodevelopment and majority may have freedom from spasms [30]. This is illustrated by an Israeli study of 37 children with cryptogenic etiology who were treated with ACTH and followed for 21 years after spasm onset [19]. All 22 children whose treatment was initiated within one month of the first appearance of spasms achieved a normal cognitive outcome, whereas normal cognition was seen in only 40% of those who started treatment later.

In a Finnish cohort of 214 patients who were also treated with ACTH, the mortality rate was 31% in the first two years of life. Of the 147 surviving patients, follow up was performed for 35 years, showing that 25% of patients had an IQ above 70, and only 36% were seizure free. Those patients who responded well to therapy, normal intellectual outcome was achieved in 70% of cryptogenic cases, but only 23% in symptomatic cases. Effective treatment in West syndrome of unknown etiology was also supported by the UKISS study, comparing vigabatrin with steroids. It was noticed that rapid treatment initiation and also a later age at onset were both significantly associated with better developmental outcomes at four years. The best outcome was noticed in patients with unknown etiology and treated by steroids.

In some symptomatic subgroups, could achieve freedom from spasms and epilepsy may be achieved in up to 50% of cases [30]. Approximately, 20% of patients have an almost normal cognitive outcome. For example, children who had a stroke or infarct respond to treatment as well as children with unknown etiology [19]. Individuals with tuberous sclerosis complex, effectiveness of seizure control and long-term development is not straightforward. In the TOSCA study of 259 patients with tuberous sclerosis complex and West syndrome, 85% of patients had controlled seizures, however only 23,5% had a normal intellectual outcome.

7.3 Lennox-Gastaut syndrome

7.3.1 Definition

Lennox-Gastaut syndrome is defined by onset before the age of 8 years, commonly starting 4 years of age with a triad of signs including multiple seizure types, on EEG slow <3 Hz spike-wave-complexes and cognitive impairment [19]. The exact diagnostic criteria are still on debate.

However, stricter criteria also include tonic seizures with EEG showing fast rhythms.

Approximately, 20% of patients with early infantile epileptic encephalopathy evolve into West syndrome and finally into Lennox-Gastaut syndrome. This shows how brain maturation may be the reason for syndrome to evolve.

7.3.2 Etiology

Etiology is classified into two groups: identifiable and unknown origin [31]. Identifiable causes include genetic, structural and metabolic causes. Approximately 70% of patients have an identifiable etiology, for instance brain damage due birth asphyxia or head injuries. Other identifiable causes may include tuberous sclerosis complex, congenital central nervous system infections, brain malformations and hereditary metabolic disorders, as in West syndrome. Perinatal complications are the most common among identifiable etiologies. The key tool for etiological evaluation is MRI, which can detect even subtle changes in brain.

Approximately, 30% of patients have a cryptogenic etiology. However, the results depend on which diagnostic modalities are used, as one of the study showed that 70% of patients had a cryptogenic etiology. Studies focusing on the phenotypes of cryptogenic cases showed that patients had a wide age range at onset, were more found commonly in male, and 30% had normal development before seizures started [31], [19]. Nowadays, it is thought that these unknown cases are possibly due to the genetic causes. In different studies, associations have been found between Lennox-Gastaut syndrome and for instance, copy number variants, SCN1A and CHD2 mutations.

7.3.3 EEG

In Lennox-Gastaut syndrome, background activity is characterized by an increase in slow waves, with slow or even absent posterior dominant rhythm [31]. However, the most characteristic finding on EEG is slow spike-and-wave complexes (SSW) at <2,5Hz, together with this abnormal slow background activity. SSW may come and go irregularly and do not necessarily have a clear onset or endpoint. Due to this, it is difficult to distinguish whether the discharges are occurring ictally or

interictally. However, clinically clear atypical absence seizures are always accompanied by SSW discharges. It is important to note that not all patients have SSW discharges, as one study showed that approximately 13% of patients did not have SSW on EEG.

Another characteristic finding on EEG is generalized paroxysmal fast activity (GPFA) which is seen as a discharge of diffuse or fast bilateral rhythms at 10-25Hz [31]. Typically GPFA appears during slow-wave sleep. These discharges typically last for a few seconds but tend to regenerate at short intervals and are commonly almost identical to each other.

Different EEG changes are seen in Lennox-Gastaut syndrome over time, according to different studies [32]. One study, called Yagi's series, reported that diffuse slow spike-and-wave pattern disappeared first during wakefulness. However, during sleep, these discharges persisted for several years. Another study, a 10-year follow-up of patients with LGS, showed that 39% of patient who had frequent epileptiform discharges was associated with poor seizure outcome. A longer follow-up study found that the slow spike-and-wave pattern disappeared after 16 years of age, but background activity gradually slowed, and the remaining interictal abnormality was often focal discharges.

A study which compromised 27 adult patients with LGS, found that background activity normalized in 44% of cases, and 74% had a reduction in epileptiform changes on EEG during wakefulness over the years. However, diffuse fast rhythms during sleep, commonly linked to tonic seizures, persisted in all patients into adulthood.

7.3.4 Seizures

The most common seizure type is tonic seizures in Lennox-Gastaut syndrome [31]. Tonic seizures are often considered essential for making the diagnosis. However, it is important to note that even though this seizure type is seen in all patients, it may not always be present at the onset of this syndrome. Tonic seizures are common, but they can be missed easily because they may be very subtle and often occurs during non-REM sleep. Hence, EEG recording during sleep is crucial.

Another very common seizure type is atypical absence seizures [31]. Recognition of these seizures is commonly difficult and frequency estimation is impossible as seizures typically start and end gradually, and many patients are already having impairment of cognitive function, hence limiting the responsiveness. Therefore, EEG monitoring is the main tool to be used, when atypical absence seizures are suspected in LGS patients.

Approximately, more than 50% of patients with LGS have epileptic drop attacks [31]. Epileptic drop attacks are dangerous and can be caused by tonic, atonic or myoclonic seizures. Drop attacks are not specific to LGS, as they can also appear in other epileptic syndromes.

Nonconvulsive status epilepticus is seen in more than 60% of patients with LGS [31]. Most commonly, it consists of prolonged atypical absences with changes in awareness and frequently interrupted by tonic seizures. The duration ranges from hours to weeks and recognition is difficult in severely cognitively impaired patients. Nonconvulsive status epilepticus is strongly associated with intellectual impairment and may contribute to its progression.

Myoclonic seizures, focal seizures, generalized tonic-clonic seizures and unilateral clonic seizures are also common in LGS [31]. These seizures often appear later when LGS evolves, but sometimes they can occur as the first seizure type, making diagnosing sometimes challenging.

A retrospective study evaluated seizure evolution in 27 patients with LGS [32]. From the early stage of LGS, all patients had tonic seizures during wakefulness and sleep. Atypical absence seizures occurred in 20/27 of patients, 12/27 of patients had atonic seizures, 9/27 had generalized tonic-clonic seizures.

Later in the follow-up, it was noticed that the amount of tonic seizures during wakefulness decreased in approximately 50% of cases. However, tonic seizures occurring during sleep were still present in all patients. Atypical absence seizures also became less frequent, persisting in only 6/27 of patients at follow-up. Atonic seizures were found in 4/27 of patients. Other seizure types occurred at the same frequency and did not show any decrease.

7.3.5 Long-term outcome

Lennox-Gastaut syndrome is known to have a negative effect on cognitive outcome [31]. At the time of diagnosis, up to 60% of individuals already have cognitive impairment. Over time, cognitive impairment tends to worsen, and after five years from the onset, 75-99% of individuals are suffering severe intellectual disability. The rest of the individuals are considered to have normal cognitive function; however, these individuals may struggle with daily functioning due to slowed mental processing. Later age at seizure onset is linked to better cognitive outcomes.

LGS patients along with cognitive impairment, have also behavioral and psychiatric problems. Attention problems, aggression and autistic behaviors are common and can cause difficulties for families and caregivers. These behavioral problems may be due to epilepsy itself, structural abnormalities of the brain, and adverse effects of the antiepileptic medications.

The long-term outcome of Lennox-Gastaut syndrome is usually poor and complete seizure remission is uncommon [31]. It negatively affects cognitive and social functioning, and living independently is rare. A cohort study of 68 individuals with LGS followed for approximately 19 years reported that there was changes in seizure types and on EEG patterns with age. Frequency and intensity of the seizures decreased; however, many patients were not seizure-free. Most commonly the seizure type which tended to persist were tonic or tonic-clonic seizures. Cognitive outcome was poor, as 94,7% had moderate to severe intellectual disability.

7.4 Epilepsy with myoclonic atonic seizures (EMAS)/ Doose syndrome

7.4.1 Definition

Epilepsy with myoclonic-atonic seizures, formerly called myoclonic-astatic epilepsy and before that Doose syndrome, often starts between 1 and 6 years of age in children who have previously had normal development [19]. The characteristic seizure type is the myoclonic-atonic seizure, which consists of symmetrical myoclonic jerks and then followed by loss of muscle tone. However, this atonic phase is sometimes difficult to evaluate after the myoclonic phase. Seizures may be frequent and may lead to status epilepticus.

Other seizure types may also occur, for instance atypical absences and generalized tonic-clonic seizures. However, it is important to note that tonic seizures and fast sleep rhythms on EEG should be absent on EMAS, as these findings are characteristic of Lennox-Gastaut syndrome.

7.4.2 Etiology

EMAS etiology is commonly unknown, although genetic factors are thought to play an important role as epilepsy is quite common in the families of affected children [19]. However the genetics are often complex and genetic testing is commonly found normal in many cases.

There two exceptions related to genetic etiology have been identified. The first one is EMAS occurring in children with febrile seizures and a family history suggesting inheritance in autosomal dominant pattern. EMAS is one of the phenotypes within genetic epilepsy with febrile seizure plus (GEFS+), where certain pathogenic variants have been recognized for instance in the SCN1A and SCN1B genes.

The second exception is glucose transporter-1 deficiency syndrome which is due to a pathogenic variant in SLC2A1 gene and presents commonly as EMAS. A GLUT-1 diagnosis may be made if

individual is has generalized myoclonic seizures and absences, a 3-Hz spike-wave-pattern on EEG, and poor response to antiepileptic medications. Ketogenic diet is a highly effective treatment for GLUT-1 related epilepsy, and it is also beneficial for many EMAS individuals even etiology is not known.

7.4.3 EEG

Interictally, meaning between seizures, EEG typically shows normal appropriate for age background activity and posterior dominant rhythm when seizure starts [33]. Characteristic feature in epilepsy with myoclonic atonic seizure is the disappearance of monomorphic biparietal theta rhythms and occipital 4Hz rhythm on EEG when the eyes are opened. However, this is not seen in all patients. Increased seizure frequency may lead to higher-amplitude background slowing.

For diagnosing this syndrome, generalized bursts of 2-6 Hz spike-wave or polyspike-waves, which may be enhanced by sleep, is mandatory. However, these may occur without any clinical manifestations. Generalized discharges may be scattered, without a focal spike focus.

Hyperventilation may enhance generalized spike-wave discharges and also absence seizures.

Photosensitivity is uncommon.

Ictally, during myoclonic-atonic seizures, EEG shows generalized spike- or polyspike-wave when individual is having myoclonic phase. This is followed by the atonic phase, which shows prominent slow wave on EEG.

Approximately 60% of children with EMAS will gain remission within 3 years after seizure onset [33]. Only those children who had remission on this syndrome was showing normalization on EEG [34].

7.4.4 Seizures

As mentioned before, myoclonic-atonic seizures are the most common type of seizure as the syndrome name says and it is mandatory for diagnosis [33]. Clinically it is seen as brief, single or occurring repeatedly myoclonic jerks which commonly affects in proximal muscles. Additionally, they are often accompanied by slight vocal sound and followed by brief atonic phase and leads to for instance head nod or sometimes an abrupt fall. In some cases, the myoclonic phase does not occur at all before the atonic phase, therefore there is a brief abrupt loss of axial tone leading to, for instance a head nods or sudden falls. Sometimes it is hard to distinguish myoclonic-atonic falls from pure atonic falls, and both seizure types may be present in the same child. The myoclonic jerk

might in some cases be so mild that it may not produce clear post-myoclonic inhibition, hence not necessarily leading to a fall.

Other seizure types may be included in this syndrome, such as absence seizures and generalized tonic-clonic seizures [33]. Generalized tonic-clonic seizure are seen in approximately 70% of children as the first manifestation of this syndrome. They can occur with or without fever and the appearance may often look like a "vibratory" type of movement especially in older patients. In some patients tonic seizures may develop later.

Approximately 17-40% of patients will have episodes of non-convulsive status epilepticus and it may be the first manifestation of the syndrome[33]. It is characterized as stupor with impaired awareness and could last from hours to days. It is often accompanied with mixture of absence, myoclonic and atonic features and additionally with drowsiness, unsteadiness, drooling, speech difficulties and unpredictable myoclonus. Intensity is typically fluctuating and may gradually intensify over time.

Roughly 33% of patients will go through a "stormy phase" [33]. It is clinically marked by very frequent seizures with multiple seizure types, most commonly generalized tonic-clonic and myoclonic seizures, escalating to non-convulsive status epilepticus. This stormy phase is typically seen within 3 months after the first seizure appears.

Overall, seizures are highly drug resistant, especially during the stormy phase [33]. However, approximately 70% of children will eventually enter remission, commonly within three years of seizure onset.

7.4.5 Long-term outcome

Development and cognitive function are typically normal, but impairments may develop at or after seizure onset [35]. Even though EMAS is classified as DEE, clinical manifestations vary enormously between patients [36]. Therefore, outcomes of cognitive function can also vary from normal development to severe intellectual impairment. Attention deficit hyperactivity disorder and autism spectrum disorder and impairments in executive functions are common comorbidities.

As mentioned before, outcomes of EMAS are very variable [33]. Individuals may have spontaneous remission with normal development or have severe seizures accompanied by moderate to severe intellectual impairment. Approximately, 70% of patients will have total remission of seizures and they can discontinue using antiepileptic medications. Among those who reach full remission, more than 50% have normal developmental progress. However, from those patients, 25% are going to

have some type of learning difficulties without intellectual disability. In those cases, when seizures continue after 5 years and additionally shows abnormalities on EEG, those patients are unlikely to achieve sustained long-term remission. This underlines the importance of correct syndrome diagnosis and initiation of effective treatment, as it may improve long-term prognosis.

There are studies which have suggested several factors to be linked to a lower probability of seizure remission and poor cognitive function [33]. These are tonic and absence seizures, prolonged or recurrent non-convulsive status epilepticus, generalized tonic-clonic seizures within the first two years of life, sleep-onset seizures, very early onset of seizures occurring before 12 months and treatment resistance. On EEG, poor prognostic factors are frequent generalized discharges, focal spikes, paroxysmal fast activity and abnormal background activity. However, these results are from different studies and may include patients with Lennox-Gastaut syndrome or some other syndromes that can have similar types of seizure patterns. Even so, one study showed that initiating the ketogenic diet as soon as possible, when three or fewer antiepileptic medications were not working, was linked to better remission rates of seizures and better developmental and cognitive outcomes than if the ketogenic diet was started later.

7.5 Landau-Kleffner syndrome

7.5.1 Definition

Landau-Kleffner syndrome (LKS) is a childhood focal epilepsy and it is one of the forms of Epileptic encephalopathy with continuous spike-waves during slow-wave sleep (CSWS), which is a spectrum of different epileptic conditions [37]. Typical onset is at the age of 3-8 years with children whose development was previously normal [38]. LKS is defined by two key features, where the first is a child developing new cognitive or behavioral impairment which is due to abundant interictal epileptiform discharges during sleep [19]. The second is that EEG shows focal interictal epileptiform activity when the patient is awake and it is strongly activated and spreads over the whole scalp during NREM sleep.

LKS is strongly characterized by loss of the ability to understand and use spoken language, called verbal auditory agnosia [19]. Other possible cognitive or behavioral characteristics may be selective deficits for instance expressive language difficulties which includes speech dyspraxia and dysarthria. Other impairments could be frontal lobe dysfunction, hemineglect, visual agnosia, arrest of learning or global cognitive decline.

LKS is not defined by the presence of the clinical seizures because in some cases seizures may be absent, even though most of the patients have seizures [19]. Clinical seizures commonly start in infancy and tend to go into remission in adolescence. Cognitive impairment often appears between four to eight years of age. Syndrome is described as having three stages: The prodromal stage, the time period from seizure onset until to age of neuropsychological regression. The acute phase, a time from regression to freedom from seizures and the residual phase which accounts time after freedom of seizures.

7.5.2 Etiology

The precise etiology of Landau-Kleffner syndrome remains unclear [38]. Brain imaging is often normal [38],[39]. There has been noted to be an association with genetic etiology, for instance with pathogenic variants in GRIN2A [40]. This gene encodes the protein GluN2A which is a subunit of the N-methyl-D-aspartate glutamate receptor. GluN2A is highly expressed in locations that are important for speech and language and NMDA receptors are crucial for learning and memory. Additionally, GRIN2A mutations are linked to other neurodevelopmental disorders and epilepsy may be one of the clinical manifestations.

Autoimmune factors have also been proposed to be a possible etiology [38]. Some of the studies have reported autoantibodies against brain-derived neurotrophic factor (BDNF) in children with Landau-Kleffner syndrome. This could explain why many patients respond well to corticosteroid treatment.

7.5.3 EEG

EEG recording is important both during awake state and during sleep [38]. When the patient is awake, EEG shows prominent uni- or bilateral discharges over the posterior temporal areas around the Sylvian fissure. These discharges start to spread widely and become more intensified during NREM sleep and evolve into an almost continuous spike-wave pattern at about 1,5-2,5Hz. Background activity and sleep macroarchitecture are normal. During REM sleep, epileptic discharges often decrease or even disappear.

The severity of abnormalities of the EEG depends on the stage of the syndrome and most commonly it is greatest at the time of syndrome onset [39]. Landau-Kleffner syndrome has a good prognosis and EEG abnormalities tend to decrease or disappear by 15 years of age with proper

treatment. However, a long history of EEG abnormalities is one of the poor prognostic factors for this syndrome.

7.5.4 Seizures

Clinically, seizures are seen in approximately 70-80% of patients with Landau-Kleffner syndrome [40]. Seizures are typically mild and may start before the language impairment in approximately 20% of cases, at the same time as language impairment, or after it in 20-30% of cases. Several seizure types are described, most commonly focal motor seizures, generalized tonic-clonic seizures and atypical absence seizures [38]. Frequency of seizures varies, but usually they are infrequent and often occur during the night [40].

7.5.5 Long-term outcome

Landau-Kleffner syndrome should be considered in a child who had previously normal development and who experiences abrupt language impairment [39]. From days to months, the child may develop verbal and/or auditory agnosia which means partial or complete inability to recognize, process and understand spoken language or some other sounds. In some cases, it is misdiagnosed as acquired deafness but hearing tests ultimately show that the peripheral hearing is normal [40].

Production of speech is also commonly affected, showing difficulties in articulation, fluency and finding words [39]. Other signs may be babbling, making up new words, repeating the same words, or sometimes even mutism. Approximately, 10% of cases have mainly expressive language impairment, however a combination of expressive and receptive impairments is more common. Language impairments have a lot of variation, even in individually, and it may fluctuate over time. There has not been found any strong correlation between clinical seizures and language impairment as even children without clinical seizures can have severe language impairment. The language impairment is thought to be due to epileptic activity in the surrounding areas of the Sylvian fissure, which is an important region for language processing. It has been noticed, that if this epileptic activity occurs during the critical stage of brain development, when synaptogenesis and long-term functional networks are formed, it may lead to persistent language impairment.

Aphasia is commonly accompanied by difficulties in social cognition and behavioral disorders including attention deficit, hyperactivity and distractibility. Emotional instability, anxiety,

depression, sleep problems, impaired working memory with preserved long-term memory are also not rare comorbidities in Landau-Kleffner syndrome [38].

In Landau-Kleffner syndrome, seizures tend to have a favorable outcome and most patients become seizure-free with antiepileptic medications [39]. In most cases, seizures and abnormal activity on EEG lessen or even disappears by around 15 years of age. Overall intelligence is usually preserved.

There is more variation in language impairments and the prognosis can be very different [39]. In adolescence, some individuals recover to normal or near normal language function, some have moderate long-term language impairments and others are left with severe receptive and expressive language impairments. For those with severe deficits it is important to introduce alternative communication methods as early as possible.

Poor prognostic factors have been noted to include early age of onset and prolonged epileptiform discharges on EEG [39]. In contrast, favourable outcomes is seen when the individual has fluctuations in the disease course.

8 Emerging syndromes

8.1 Developmental and epileptic encephalopathy with spike-wave activation in sleep (DEE-SWAS)

8.1.1 Definition

Developmental and epileptic encephalopathy with spike-wave activation in sleep is a spectrum of disorders whose hallmark is spike-wave activation during NREM sleep and it is associated with regression in cognition, language, behavior and motor function [41].

8.1.2 Clinical features in childhood

This syndrome commonly begins between 2 and 12 years of age, with a peak occurring at 4-5 years of age and it affects both males and females [2]. In DEE-SWAS, there is neurodevelopmental impairment prior to the regression. Regression can occur in cognition, behavior, psychiatric function and in motor function, and emerges approximately 1-2 years after seizure onset. Seizures are commonly focal and occur during the night, however atypical absences, atonic seizures, negative myoclonus and generalized tonic-clonic seizures can also be present [42].

8.1.3 Long-term outcome

In DEE-SWAS, seizures and spike-wave activation in sleep (SWAS) often resolve after puberty, but neurocognitive deficits often remains unfavorable [2]. Studies have shown that during the active phase of this syndrome, IQ markedly declines [43]. After remission of SWAS, developmental outcomes vary from partial cognitive improvement to those patients whose cognition continued to decline. Although some improvement may occur over time, residual deficits commonly persist [2]. Early onset of SWAS was linked with poorer neurodevelopmental outcome [43].

8.2 Febrile infection-related epilepsy syndrome (FIRES)

8.2.1 Definition

Febrile infection-related epilepsy syndrome is a subcategory of new-onset refractory status epilepticus (NORSE) in which refractory status epilepticus occurs after a febrile infection [2]. It occurs predominantly in children and adolescents. The etiology is not known.

8.2.2 Clinical features in childhood

Syndrome begins commonly between 2-17 years of age, peaking approximately at 8 years of age and shows slightly male predominance [2]. Prior development is usually normal. FIRES is triggered by febrile illness most often upper respiratory infection or gastrointestinal infection.

Seizures typically start 24h to 2 weeks after the illness. Seizures are focal or multifocal and it may include focal to bilateral tonic-clonic seizures. Seizures and encephalopathy develop rapidly with seizures increasing in frequency over days to weeks and becoming highly drug resistant. Seizures often progress to super-refractory status epilepticus.

This acute phase may last from 1-12 weeks and often requires prolonged intensive care treatment. Approximately 10% of patients do not survive from this stage. The acute phase is followed by a chronic phase, where patients develop drug-resistant multifocal epilepsy with intellectual impairment. EEG shows background slowing and multifocal epileptiform abnormalities.

8.2.3 Long-term outcome

The overall outcome is often poor with significant mortality and persistent morbidity [44]. In a pediatric cohort, in-hospital mortality was 16% and all those patients who survived developed drug-

resistant epilepsy and needed long-term antiseizure medication polytherapy. Cognitive deficits were present in 61% of cases, although some improvement may occur over time.

Poorer outcome has been linked to with younger age at onset and longer duration of medically induced burst-suppression coma [2]. Additionally, attentional and behavioral challenges, including aggression as well as motor abnormalities are also common.

8.3 Epilepsy of infancy with migrating focal seizures (EIMFS)

8.3.1 Definition

Epilepsy of infancy with migrating focal seizures is a rare and severe syndrome and it is part of the developmental and epileptic encephalopathy group [2]. It is characterized by recurrent focal seizures which lead to severe neurodevelopmental impairment. Etiology is commonly due to de novo gene abnormalities, however inheritance of a mutated gene of KCNT1 have been reported.

8.3.2 Clinical features in childhood

This syndrome commonly starts during the first six months of life, peaking at 3 months of age, although the onset can vary within the first year [2]. It affects males and females equally. Development is often normal, however over time most children develop microcephaly, most commonly by 1 year of age. Even though development may be normal at onset, regression is common after seizure onset.

Seizures arise independently from both hemispheres and can migrate between different cortical regions [2]. Mandatory seizure types for this syndrome are focal motor seizures, either clonic or tonic. Seizures tend to be infrequent in the beginning but typically increase in frequency with time. It is mandatory for this syndrome to have clinical or EEG signs that the seizure activity migrates. Clinically, this may be seen when seizure starts with focal motor features on one side of the body, then it stops briefly and appears on the other side of the body.

Ictally, EEG shows activity independently in different cortical regions which confirms the migrating pattern, needed for this syndrome. EEG abnormalities are often more prominent during sleep deprivation, drowsiness and sleep.

8.3.3 Long-term outcome

The prognosis is generally poor as most patients will have intractable seizures with severe neurological impairment and reduced life expectancy [2]. Follow-up studies have described additional neurological and systemic problems for instance movement disorders, hypotonia, severe language impairment and gastrointestinal dysmotility [45]. Although some children may show some improvement in seizures, developmental outcome often remains severely affected [46]. In patients with KCNT1 gene mutations, prognosis is poor and severe, with ongoing epilepsy, high mortality and additionally reported cases of sudden unexpected death in epilepsy.

8.4 Self-limited familial neonatal-infantile epilepsy (SeLFNIE)

8.4.1 Definition

Self-limited familial neonatal-infantile epilepsy syndrome is an autosomal dominant familial focal epilepsy in which seizures begin in the neonatal or infantile period [2]. This syndrome can be differentiated from self-limited familial neonatal epilepsy and self-limited familial infantile epilepsy when the family history shows that some individuals in the family had seizure onset in the neonatal period and others in the infantile period.

8.4.2 Clinical features in childhood

In this syndrome the onset of focal seizures varies from the first day of life to 23 months of age [2]. Males and females are affected equally. Prior history and development are usually normal. Seizures are typically focal motor seizures, either tonic or clonic and they may occur in clusters lasting from hours to days.

8.4.3 Long-term outcome

Although the long-term outcome in SeLFNIE is generally good, the outcome is not always entirely benign [47]. Most patients have average adaptive functioning and achieve remission in seizures, but some individuals may later develop recurrent seizures many years after epilepsy has resolved. Additionally, minority have developmental difficulties, including global developmental delay and autism spectrum disorder. Poorer outcome has been noticed in patients who have higher seizure burden and a longer duration of epilepsy. Overall, the frequency of seizures differs between affected individuals, but most often seizures remit by 12-24 months of age [2].

9 Discussion

On this review, one of the findings is that childhood-onset epilepsies especially developmental and epileptic encephalopathies, change a lot over time. The clinical picture seen in adulthood is often very different from what is seen in childhood. Seizure frequency or even seizure type may change and EEG findings may improve. However, many patients continue to have cognitive, behavioral, motor, or language difficulties after seizure frequency has decreased. This underlines the fact that not only seizures affect the long-term outcome.

Another important aspect is the strong role of etiology. The underlying cause often has a significant effect on prognosis. This was for instance noticed in West syndrome, where children with cryptogenic etiology had generally a better outcome than those with a structural or other identified cause. In genetic epilepsies for instance in Dravet syndrome, the gene defect not only causes seizures but also affects development more directly. Due to this, the long-term outcome in many DEEs is not explained by seizures alone but by the combination of developmental vulnerability and epileptic activity.

This review also showed that improvement in seizures does not necessarily mean improvement in overall functioning. In Dravet syndrome, seizure frequency may become lower with age but intellectual disability, motor difficulties and dependence on others usually remain. In Lennox-Gastaut syndrome, seizure types may evolve and abnormalities on EEG may lessen but the outcome is still often poor. In Landau-Kleffner syndrome, seizures tend to ease, but language impairment may continue to affect patients for several years.

Early diagnosis and treatment are also important factors. Especially in West syndrome, earlier treatment is associated with better developmental outcome. The same effect was also seen in EMAS, where early proper diagnosis and treatment initiated as quickly as possible may improve long-term outcome. This shows how delaying treatment in the developing brain may allow to epileptic activity to cause more lasting harm.

This literature review also has limitations. Many studies were retrospective and included small patient groups or combined patients with different etiologies. This makes it harder to compare results across studies. For some rare syndromes, there was limited data concerning adult follow-up, so the conclusions about adulthood outcomes were based on a small number of reports. In addition, due to classification systems and diagnostic methods have changed over time, older and newer studies are not necessarily fully comparable.

Even though there are these limitations, there is still consistency. Childhood-onset epilepsies often continue to adulthood, even when seizures improve. Due to this, long-term care should also focus on other aspects for instance cognition, language, behavior, education and psychosocial functioning. This is important especially when children with complex epilepsy syndromes transition from pediatric to adult care.

In the future, more long-term studies are needed, especially studies that focus on following patients from childhood to adulthood. More information is needed about adult functioning, psychiatric symptoms, independence and quality of life.

In conclusion, this review shows that childhood-onset epilepsies are not only childhood conditions but often lifelong disorders. Even when seizures become less severe or less frequent, many patients continue to have significant difficulties in adulthood. For that reason long-term outcome should be assessed more widely than good seizure control alone.

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