Université Libanaise

École Doctorale
Sciences et Technologies

Université de Limoges

THESE de doctorat en Cotutelle

Pour obtenir le grade de Docteur délivré par

L'Université Libanaise

L'Ecole Doctorale des Sciences et Technologie

Spécialité : Recherche Clinique

Présentée et soutenue publiquement par

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Le 30 Octobre 2023

Management of pediatric epilepsy in Lebanon: Evaluation of factors affecting seizure control, psychiatric comorbidity, quality of life and adherence to treatment

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Ph.D. Thesis

Université de Limoges

University of Limoges

École Doctorale Biologie, Chimie, Santé

NET - UMR INSERM-CHU 1094

A thesis submitted to University of Limoges
in partial fulfillment of the requirements of the degree of

Doctor of Philosophy

Santé publique, épidémiologie, environnement et sociétés

Presented and defensed by

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On 30 October 2023

Management of pediatric epilepsy in Lebanon: Evaluation of factors affecting seizure control, psychiatric comorbidity, quality of life and adherence to treatment

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Dedication

To my lovely family.

Acknowledgements

I would like to express my heartfelt gratitude to my esteemed thesis supervisors for their valuable guidance, unwavering support, and immense dedication throughout the journey of completing this thesis. Their expertise and encouragement have been instrumental in shaping this research and helping me reach the finish line.

First and foremost, I extend my deepest appreciation to **Prof. Amal Al-Hajje**, whose depth of knowledge and commitment to academic excellence have been a constant source of inspiration in my academic life.

I would also like to extend my gratitude to **Prof. Farid Boumediene**, whose expertise and unique perspective have been invaluable assets to this research. Your guidance and support at every step of the process has been truly remarkable, and I am sincerely grateful for your mentorship.

I am thankful to my thesis co-directors **Prof. Pascale Salameh** and **Dr. Jeremy Jost** for their insightful comments and constructive criticism which has been pivotal in strengthening the quality of this work.

Furthermore, I would like to thank **Prof. Ahmad Beydoun** whose mentorship and profound experience in the field of epilepsy provided valuable clinical insights that enriched the study design and interpretation of results. His unwavering dedication and passion for research was an inspiration throughout this project.

I would like to extend my gratitude to the reviewers and examiners of this thesis: **Prof. Wissam Faour, Prof. Stephane Auvin, Prof. Alessandra Nicoletti,** and **Dr. Sahar Farhat.** Thank you for contributing your time, experience, and insights to evaluate and review my dissertation. Your constructive feedback and suggestions will significantly enrich the quality of my research and contribute to the successful completion of this work.

Last but not least, I am grateful for my family for unwavering encouragement and understanding throughout this academic journey. Their love and belief in me have been a constant source of motivation.

In conclusion, I am truly fortunate to have had such exceptional supervisors guiding me throughout this thesis. Their expertise, dedication, and encouragement have been instrumental in the successful completion of this work.

Thank you.

Rights

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Abbreviations

Self-limited focal epilepsies	(SeLFE)
Genetic generalized epilepsies	(GGE)
Developmental and/or epileptic encephalopathies	(DEE)
Electroencephalogram	(EEG)
Self-limited epilepsy with centrotemporal spikes	(SLECTS)
Self-limited epilepsy with autonomic seizures	(SeLEAS)
Childhood occipital visual epilepsy	(COVE)
Photosensitive occipital lobe epilepsy	(POLE)
Childhood Absence Epilepsy	(CAE)
Juvenile Absence Epilepsy	(JAE)
Juvenile Myoclonic Epilepsy	(JME)
Epilepsy with Generalized Tonic Clonic Seizures Alone	(EGTCS)
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Developmental and/or epileptic encephalopathy with spike-and-wave activation in sleep	(DEE-SWAS)
Magnetic resonance imaging	(MRI)
National Institute for Health and Care Excellence	(NICE)
Anti-seizure medications	(ASMs)
Drug resistant epilepsy	(DRE)
P-glycoprotein	(P-gp)
Multidrug resistance-associated proteins	(MRP)
Health related quality of life	(HRQL)
American University of Beirut Medical Center	(AUBMC)
Two-year remission	(2YR)
Intellectual and developmental delay	(IDD)
Interictal epileptiform discharges	(IEDs)
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Focal impaired awareness seizures	(FIAS)

Focal to bilateral tonic-clonic seizures	(FBTC)
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Generalized onset tonic-clonic seizures	(GOTC)
Myoclonic epilepsy in infancy	(MEI)
Attention deficit hyperactive disorder	(ADHD)

Abstract

Introduction: Epilepsy is recognized as one of the most prevalent neurological condition in childhood. Although many children with epilepsy respond favorably to antiseizure medications (ASMs), almost one third of children have drug resistance. Children with uncontrolled seizures suffer a wide range of comorbidities and have an increased risk of mortality. The aim of this study was to evaluate early baseline predictors of two year remission; predictors of drug resistance in different epilepsy syndromes; and factors associated to psychiatric comorbidity in a large cohort of children with new-onset seizures.

Methodology: A propspective cohort of children with newly diagnosed epilepsy was identified at the American Univeristy of Beirut Medical Center. Survival analysis and recursive partition analysis were performed to find the determinants of seizure remission. Multivariable logistic regression was performed to find predictors of drug resistance and associates of psychiatric comorbidity.

Results: Intellectual and developmental delay (IDD) was the most important predictor of non-remission. An epileptogenic lesion was a significant predictor of non-remission only in patients without evidence of IDD, and a high number of pretreatment seizures was a predictive factor in children without IDD and in the absence of an epileptogenic lesion. Concerning predictors of drug resistance, within the genetic generalized epilepsies, factors associated with drug resistance were younger age at seizure onset and experiencing multiple seizure types. Within the focal non-maturational epilepsy, younger age at epilepsy onset, detection of an epileptogenic lesion on brain MRI, experiencing multiple seizure types, and having a greater number of pretreatment seizures were significant predictors of drug resistance. Within the developmental and epileptic encephalopathies, experiencing tonic or focal impaired awarness seizures predicted drug resistance. Concerning psychiatric comorbidity, the most important factors associated with occurrence of internalizing psychiatric comorbidity was treatment failure (failure of at least two ASMs), while IDD was the most important associated factor with externalizing psychiatric comorbidity.

Conclusion: Our results indicate that it is possible to identify patients at risk of not achieving a remission based on variables obtained at the initial evaluation. This could allow for a timely selection of patients who require close follow-up, consideration for neurosurgical intervention, or investigational treatments trials. In addition, different epilepsy syndromes have different predictors of drug resistance. Psychiatric comorbidity should also be routinely evaluated in children with epilepsy, especially in those suffering poor seizure control or IDD.

Chapter I. Introduction

I.1. Background

Epilepsy is the most common neurological disorder in children, affecting one percent to two percent of the pediatric population (1) . Epilepsy can be conceptually defined by the occurrence of seizures. However, seizures are just one of the manifestations of epilepsy. Epilepsy goes well beyond seizures, as it is accompanied by a wide range of cognitive, behavioral, and psychiatric disorders that may be just as troubling, if not more for the patients and the family.

Interestingly, these complications may be mitigated by appropriate therapeutic interventions, achieving seizure control early in the course of the disease, and by early referral of children who are candidates for epilepsy surgery. A comprehensive and effective approach to treating and managing epilepsy therefore requires early identification of children at risk of having poor seizure control, in addition to addressing epilepsy comorbidities to improve overall outcome.

I.2. Epilepsy definition

Epilepsy was conceptually defined as a disorder of the brain characterized by an enduring predisposition to epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition (2). The operational definition proposed by the International League Against Epilepsy (ILAE), used for purposes of clinical diagnosis, considers epilepsy to be a disease of the brain defined by any of the following conditions: [1] At least two unprovoked (or reflex) seizures occurring >24 h apart; [2] one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; [3] diagnosis of an epilepsy syndrome (3).

I.3. Incidence and prevalence of epilepsy in childhood

Epilepsy is considered the most chronic and recurrent neurologic condition in childhood, affecting 0.5% to 1% of children (4). The worldwide incidence of epilepsy in children ranges from 41-187/100,000, and the prevalence ranges from 3.2-5.5/1,000 in developed countries and 3.6-44/1,000 in underdeveloped countries (5). The incidence and prevalence of childhood epilepsy in Arab countries is poorly documented. Studies done in Egypt found a prevalence of 7.2-9.7/1000 (6,7). In Lebanon, there is a lack epidemiological studies on the prevalence of epilepsy.

I.4. **Classification of epileptic seizures**

According the 2017 ILAE operational classification of seizure types (8) (Appendix 1), the first level of classification begins by classifying seizure types according to their location of onset in the brain into either focal, generalized, or unknown onset. Focal seizures (prev. partial seizures) involve neuronal discharges in just one cerebral cortex, usually due to structural abnormalities (9). Generalized seizures involve electrical discharges that affect the cortex of both hemispheres, usually causing loss of consciousness (9). In the second classification level, generalized seizures are categorized according to the presence of motor onset, while focal seizures are classified according to the associated awareness impairment and the presence of motor or non-motor symptoms.

Focal seizures include focal aware seizures (prev. simple partial seizures); with no impairment of awareness; and focal impaired awareness seizures (prev. complex partial seizures); associated with a decreased level of awareness. Focal seizures can be followed by a generalized seizure, which is known as *secondary generalization*. This happens when a partial or focal seizure spreads to the other hemisphere, activating the entire cerebrum bilaterally. This new entity is called focal to bilateral tonic–clonic seizures (prev. partial onset seizures with secondary generalization) (8).

Generalized motor seizures include epileptic spasms, tonic-clonic, clonic, tonic, myoclonic, and atonic seizures. Generalized non-motor seizures include typical and atypical absence, myoclonic absence, and eyelid myoclonia (8).

In some instances, generalized and focal seizures may co-exist in electroencephalogram (EEG) and clinical presentation, such as in Dravet syndrome whereby the child initially presents with prolonged, febrile and afebrile hemiclonic or generalized clonic seizures. New seizure types develop between one and four years of age, including myoclonic and atypical absences, focal seizures and generalized tonic-clonic seizures (10).

I.5. **Classification of childhood epilepsies**

The ILAE published a new classification of epilepsy in 2017 (11) that not only takes into consideration the clinical semiology but also incorporates the etiology.

The 2017 multi-level classification (Appendix 2) presents with three levels. It starts with the clinical identification of seizure type (focal, generalized, or unknown onset). After diagnosis of the seizure type, the next step is diagnosis of epilepsy type, including focal epilepsy, generalized epilepsy, combined generalized, and focal epilepsy, and also an

unknown epilepsy group. The third level of 2017 ILAE classification involves the identification of a specific epilepsy syndrome, which refers to the presence of specific clinical, EEG, and imaging features. The clinician should aim to identify the etiology of the patient's epilepsy which is key in guiding the therapeutic plan. The classification system recognizes six etiologic groups: structural, genetic, infectious, metabolic, immune, and unknown (Appendix 3).

The identification of an epilepsy syndrome is critical in guiding investigations, selecting optimal therapy, and providing insight on seizure outcome and comorbidities (12). An epilepsy syndrome is defined as a characteristic cluster of clinical and EEG features, often supported by specific etiological findings (structural, genetic, metabolic, immune, and infectious) (12). In 2022, the ILAE published a classification of epilepsy syndromes with onset in childhood (13), which divides them into three categories: self-limited focal epilepsies (SeLFE); genetic generalized epilepsies (GGE), and the developmental and/or epileptic encephalopathies (DEE).

Self-limited focal epilepsies have a presumed genetic etiology. They are characterized by focal seizures and by epileptiform abnormalities on electroencephalogram (EEG) with distinctive morphology and location (depending on the epilepsy syndrome), often activated with sleep. They have an age-dependent occurrence, specific for each syndrome, and are pharmacoresponsive with remission usually spontaneously occurring by puberty. No significant structural lesion on brain magnetic resonance imaging (MRI) is detected. This group comprises four main syndromes: self-limited epilepsy with centrotemporal spikes (SLECTS, prev. benign rolandic epilepsy), self-limited epilepsy with autonomic seizures (SeLEAS, prev. Panayiotopoulos syndrome), childhood occipital visual epilepsy (COVE), and photosensitive occipital lobe epilepsy (POLE).

Genetic generalized epilepsies of childhood have a genetic etiology with complex polygenic inheritance. They are characterized by generalized seizure types and generalized spike-wave discharges on EEG. A positive family history of epilepsy is frequently found. Response to treatment is variable. GGEs are generally drug responsive but some syndromes may require life-long treatment. GGEs comprises the idiopathic generalized epilepsies consisting of four syndromes: Childhood Absence Epilepsy (CAE); Juvenile Absence Epilepsy (JAE); Juvenile Myoclonic Epilepsy (JME); and Epilepsy with Generalized Tonic Clonic Seizures Alone (EGTCS), and two additional syndromes: epilepsy with myoclonic absence (EMA); and epilepsy with eyelid myoclonia (prev. Jeavons syndromes).

Developmental and/or epileptic encephalopathies are defined as diseases in which the epileptic activity itself contributes to severe cognitive and behavioral impairments above and beyond that expected from the underlying etiology alone. These diseases are

generally pharmacoresistant and are characterized by multiple seizure types including both focal and generalized. Epileptiform activity is frequent and is associated with developmental slowing and often regression. DEEs comprise syndromes: infantile epileptic spasms syndrome (IESS, prev West syndrome), epilepsy with myoclonic–atonic seizures (EMAtS, prev. Doose syndrome), Lennox–Gastaut syndrome, developmental and/or epileptic encephalopathy with spike-and-wave activation in sleep (DEE-SWAS), hemiconvulsion–hemiplegia–epilepsy syndrome, and febrile infection related epilepsy syndrome.

Based on seizure types, epilepsy may be classified into either generalized or focal epilepsies. Focal (localization-related) epilepsies; formerly known as symptomatic epilepsy, are a distinct group of epilepsies where a structural etiology underlies epilepsy In some patients, the etiology of focal epilepsy may not be identified, in this case the epilepsy is termed focal epilepsy of unknown etiology (formerly known as cryptogenic epilepsy) (11). A structural etiology refers to abnormalities visible on structural neuroimaging where the electroclinical assessment together with the imaging findings lead to a reasonable inference that the imaging abnormality is the likely cause of the patient's seizures. Structural etiologies may be acquired such as stroke, trauma, and infection, or genetic such as malformations of cortical development or tuberous sclerosis. Despite there being a genetic basis with such malformations, the structural correlate underlies the person's epilepsy. Identification of a structural lesion requires appropriate epilepsy protocol MRI studies. Response to treatment is variable according to the type of structural lesion identified, and many patients who fail treatment may be candidate for epilepsy surgery.

I.6. **Risk factors for childhood epilepsy**

Risk factors for epilepsy are conditions that are associated with an increased likelihood of developing epilepsy. The most commonly recognized risk factors and which were confirmed by a systematic review (14) are: a family history of epilepsy, having a history of febrile seizures, central nervous system (CNS) infections (cerebral malaria, meningitis, human immunodeficiency virus), head trauma, and perinatal insult (14).

I.7. **Epilepsy diagnosis guidelines**

According to the 2022 National Institute for Health and Care Excellence (NICE) epilepsy guidelines (15), a child presenting with new onset seizures should at initial presentation be referred to a pediatrician with expertise in assessing first seizures and diagnosing epilepsy.

A detailed history of the event should be obtained from the child if possible and from a witness, including the sequence of events leading to the seizure, the presence or absence of focal features and the level of awareness throughout the seizure. Information should also be obtained about previous seizures, family history of young sudden death, epilepsy or arrhythmic disorders, developmental history and assessment of the child, and consideration of non-epileptic seizure differential diagnosis.

Diagnostic exams should be done including a detailed physical examination (temperature, blood pressure, neurological exam, cardiac exam, mental status examination…), neuroimaging (considered only when new focal deficits are noted on examination, the history or examination suggests head trauma, or following a first episode of status epilepticus), and EEG (performed after discussion with a pediatrician or pediatric neurologist if the child has had more than one epileptic seizure or a prolonged epileptic seizure). If an EEG is requested after a first seizure, perform it as soon as possible (ideally within 72 hours after the seizure).

Genetic testing can be considered after discussion with a neurologist or geneticist. Whole-genome sequencing may be considered for patients with epilepsy of unknown cause who: were aged under 2 years when epilepsy started; or have clinical features suggestive of a specific genetic epilepsy syndrome (for example, Dravet syndrome); or have additional clinical features such as: a learning disability, autism spectrum disorder, a structural abnormality (for example, dysmorphism or congenital malformation), or unexplained cognitive or memory decline.

Antibody testing should be considered in new-onset epilepsy if autoimmune encephalitis is suspected.

In patients with a confirmed epilepsy, it is necessary to determine the seizure type(s), epilepsy type, etiology, and epilepsy syndrome if possible. Classification of epilepsy should be performed using the multi-axial diagnostic scheme discussed previously (11), since failure to classify the epilepsy correctly can lead to inappropriate treatment and persistence of seizures.

A framework for the diagnosis of epilepsy is presented in Appendix 4.

I.8. **Epilepsy Management**

The primary medical goal in the management of epilepsy focuses almost exclusively on seizure control through anti-seizure medications (ASMs) with minimal or no adverse effects. ASMs are the mainstay of treatment for children with newly diagnosed epilepsy. Although ASMs may not cure the condition, patients may remain seizure-free with an

appropriate regimen. Controlling seizures can also negate the physical, psychological and social comorbidities of epilepsy (16).

Antiseizure medications are classified into old (first-) generation or new (second- and third-) generation agents (17). The first generation ASMs include phenobarbital, phenytoin, primidone, ethosuximide, valproate, carbamazepine, clonazepam, and clobazam. The second-generation ASMs (which were approved for the treatment of epilepsy since the late 1980s) include, in chronological order, vigabatrin, oxcarbazepine, lamotrigine, gabapentin, felbamate, topiramate, tiagabine, levetiracetam, and zonisamide. The third-generation ASMs include, pregabalin, fosphenytoin, lacosamide, rufinamide, eslicarbazepine, retigabine (also known as ezogabine), perampanel, brivaracetam, cannabidiol, stiripentol, cenobamate, and fenfluramine. The newer ASMs vary considerably in their mechanisms of action, spectra of activity, pharmacokinetics, and adverse effects profiles.

According to the NICE guidelines (15) for treatment of generalized tonic-clonic seizures, sodium valproate should be offered as first-line monotherapy, except in women and girls with a likelihood of pregnancy, where lamotrigine or levetiracetam should be offered as first-line monotherapy. If first-line monotherapy with sodium valproate is unsuccessful, lamotrigine or levetiracetam should be offered as second-line monotherapy treatment. If monotherapy is unsuccessful, one of the following first-line add-on treatment options should be considered: clobazam, lamotrigine, levetiracetam, perampanel, sodium valproate, or topiramate. If first-line add-on treatments tried are unsuccessful, one of the following second-line add-on treatment options should be considered: brivaracetam, lacosamide, phenobarbital, primidone, or zonisamide.

For the treatment of focal seizures with or without evolution to bilateral tonic-clonic seizures, the NICE guidelines recommend lamotrigine or levetiracetam as first-line monotherapy. If first-line monotherapies are unsuccessful, one of the following second-line monotherapy options should be considered: carbamazepine, oxcarbazepine, or zonisamide. If second-line monotherapies tried are unsuccessful, lacosamide may be considered as third-line monotherapy. If monotherapy is unsuccessful add-on treatment should be considered.

For absence seizures, ethosuximide is recommended as first-line treatment. For myoclonic seizures, tonic or atonic seizures, sodium valproate should be considered as first-line treatment. The NICE 2022 guidelines for treatment of specific seizure types and childhood epilepsy syndromes are presented in appendix 5 and 6.

Noteworthy is that ASMs present with extensive pharmacokinetic variability, resulting in pronounced differences in serum concentrations between patients (18). This variability

requires therapeutic drug monitoring to make dose adjustments based on measured drug concentrations, so as to optimize clinical outcome.

Some patients whose seizures prove difficult to treat on ASMs could benefit from non-pharmacological strategies, such as ketogenic diet, vagus nerve stimulation, or epilepsy surgery. Epilepsy surgery remains one of the most underutilized effective treatment modalities worldwide (19). Excessive delay in pursuing effective surgical therapy may risk serious psychosocial and physical disability (20). For this reason, early identification of children at risk of having poor seizure control and later developing drug resistant epilepsy is of paramount importance, as it allows giving answers to parents and more importantly, allows early identification of surgical candidates (21).

I.9. **Treatment outcome and predictive factors**

Despite the introduction of over a dozen second-generation ASMs with different mechanisms of action throughout the past 3 decades (22), long-term seizure control has not fundamentally improved (23). Around 50% patients with newly diagnosed epilepsy achieve seizure control on their first ever ASM usually at a modest or moderate dose (24). A further 10% of patients achieve seizure control on their second or third drug ASM (25). Thereafter, the likelihood of a perfect outcome becomes progressively lower with around 30% of this population developing drug resistant epilepsy (DRE) (26). DRE is defined by the ILAE as failure of adequate trials of two tolerated and appropriately chosen and used ASM schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom (21).

It is questionable why and how epilepsy becomes drug resistant, while some patients with seemingly identical seizure types are able to achieve seizure control with medication. Several possible mechanisms underlying pharmacoresistance in epilepsy have been identified in recent years. Experimental studies have put two major neuro-biologic theories; the first being efflux of ASMs from the epileptogenic tissue through excessive expression of multidrug transporters such as P-glycoprotein (P-gp) and multidrug resistance-associated proteins (MRP); and the second being reduced drug-target sensitivity in the epileptogenic tissue (27).

Epidemiological studies have also identified multiple factors that have been found to be predictive of seizure outcomes. Results from these studies are often conflicting, probably due to variability in the study population and methodologies. The main factors accumulated from different epidemiological studies include: younger age at epilepsy onset, experiencing multiple seizures types, higher initial seizure frequency, greater number of pretreatment seizures, structural brain lesion, presence of neurologic deficit,

psychiatric comorbidity, and experiencing status epilepticus. These factors are discussed below.

younger age at epilepsy onset was associated with a poorer outcome in multiple studies (28,29). Berg and colleagues found that age at onset was a predominant predictor of intractability, and noted that the predictive value of age was not only limited to children aged less than 1 year (30). Prognosis was progressively better with increasing age during childhood and adolescence. A recent meta-analysis, however, found that age at onset was not a predictor of drug resistance (31).

Children experiencing multiple seizure types also appear to have a worse outcome in numerous studies (32–34). A meta-analysis on patients with JME revealed that having three seizure types was a prognostic factor for refractoriness (35). A higher initial seizure frequency and a greater number of pretreatment seizures have also been found to have a negative impact on seizure outcome (36–40). However, a critical review of several studies (41), showed that the relationship between high initial seizure frequency and poor outcome is only true for children having FIAS. Another study also found that patients with GTCs and absence seizures had 80 and 85% probability respectively of achieving remission, compared to only 65% for patients with FAIS (42). It is thus plausible that specific seizure types play an important role in predicting seizure outcome.

It has been consistently shown that epilepsies that can be attributed to a structural brain lesions have a lower probability of entering remission (25,32,37,43–46). The nature and location of the underlying structural abnormality was also found to affect treatment outcome (47). Experimental data has shown an intralesional cell-specific predominance of multidrug resistance transporters, namely in focal cortical dysplasia and glioneuronal tumors (48,49), which may be the mechanism for intrinsic pharmacoresistance observed in patients with lesional etiology.

Many studies have also indicated that the presence of neurologic deficit, manifested as intellectual and/or developmental delay is indicative of poor prognosis (28,29,32,33,42,44). However, it seems that developmental delay doesn't alter the outcome of epilepsy by itself, but rather indicates the presence of a lesional etiology, thus reflecting an increased severity due to an underlying brain abnormality.

Another factor that is widely discussed is the presence of psychiatric comorbidity. Psychiatric cormorbidity is very common in children with epilepsy and has been associated with failure to achieve remission (35,50). It is possible that the underlying neurobiologic process underlying psychiatric comorbidity may increase brain dysfunction and therefore increase the likelihood of drug resistant epilepsy (50).

Furthermore, several studies have also indicated that children experiencing status epilepticus have an increased risk of drug resistance (29,37,51,52). Experimental studies have shown that the prolonged seizures in status epilepticus reduces expression of GABA receptors, which leads to resistance to benzodiazepines for example (53). Status epilepticus also induces overexpression of drug efflux transporters, such as P-gp which leads to resistance to drugs that are substrates for these transporters (53).

I.10. **Epilepsy comorbidities in childhood**

Epilepsy is not just a seizure disorder, as it is often accompanied by a wide range of comorbidities that complicate the management of epilepsy and significantly increases the burden of the disease (54). There exists a complex relationship between comorbid conditions and epilepsy. In some cases, the comorbid condition can be a result of epilepsy. For instance, epilepsy can lead to an anxiety disorder, depression, or sleep disorder. In other situations, a common pathophysiological substrate leading to both epilepsy and the comorbid condition may be present (55). In this case, the comorbid condition may precede the epilepsy.

Comorbidities in children with epilepsy can be broadly divided into psychological, neurological, and physical (56).

Neurological comorbidities include intellectual disability, language impairment, migraine, and sleep disorders. Intellectual disability is one of the most commonly reported epilepsy comorbidities, occurring in 30 to 40% of children with epilepsy (57). Several factors have been linked to intellectual disability including young age at epilepsy onset, symptomatic etiology, having an epileptic encephalopathy, and continued treatment with ASMs (58,59)

Psychological comorbidities occurs in around 25% of children with epilepsy and may occur independently of the seizure control (60). Psychiatric disorders comprise mood disorders (depression and anxiety), psychosis, personality change, behavioral problems, attention deficits, and autism spectrum disorder (61). Data for epidemiological studies have established a bidirectional relationship between epilepsy and psychiatric disorders, implying that either of them can precede or follow the other (62–66).

Physical comorbidities include bone loss, immunological disturbances, hypothyroidism, retardation of body height growth, dyslipidemia, and carnitine deficiency. These comorbidities may result from the disease itself or as adverse effects of ASM treatment (56).

The high frequency and deleterious impact of these comorbidities has reshaped the management of childhood epilepsy. Today, comprehensive care of epilepsy goes beyond simply attempting to control seizures with minimal adverse events. Identification and targeting epilepsy comorbidities is increasingly recognized as an integral component of epilepsy care.

I.11. **Health-related quality of life in childhood epilepsy**

Chronic diseases in general have a great impact on quality of life. Health realted quality of life (HRQL) is a multi-dimensional concept used to examine the impact of health status on quality of life (67). Children living with epilepsy are found to have reasonably more compromised HRQL, specifically in the psychological, social and school domains compared to children having other diseases such as asthma (68). These findings suggest that these problems are specific to epilepsy and not merely the result of living with a chronic condition. Children with epilepsy also often experience significant restrictions of activities because of the unpredictability of seizures, leading to lower HRQL (69). Intellectual deficit is also well reported in children with epilepsy, which influences the child's academic achievement (70).

Poorer HRQL has been associated to older age at epilepsy onset, living in rural areas, living with a caregiver with lower literacy levels, higher seizure frequency, receiving polytherapy, having focal seizures, longer duration of treatment, presence of comorbidities, and having intellectual deficit (71,72).

There exist two popular but distinct approaches to measure HRQL in children (73). The first approach involves the application of 'generic' HRQL tools. These tools provide a broad measure of HRQL regardless of the underling disorder. The Child Health Questionnaire and the Pediatric Quality of Life Inventory (PedsQL) are examples of these generic tools. Although these tools address different domains of psychosocial and physical functioning, they might lack the sensitivity to detect subtle aspects of specific conditions or disorders. The second approach involves 'Disease or condition-specific' HRQL instruments, which are created to evaluate characteristics of a particular condition and its effect on QOL (73). These instruments provide data that are more relevant and sensitive to the influence of a specific disease on QOL.

A pitfall of disease-specific instruments is that they are less widely used than generic measures, and therefore their psychometric properties and how well they perform in different populations might be not known. This addresses the need for validation of epilepsy specific quality of life measures, in different populations and in different languages, for use in routine clinic visits.

I.12. **Adherence to antiseizure medication**

The clinical factors we have mentioned above are of great importance to understand the disease course and predict prognosis, however they do not fully explain the variability in seizure outcome. An important modifiable factor influencing seizure control is adherence to treatment. Adherence to medication is defined as the extent to which a person's behavior in taking medication corresponds with the agreed recommendation from a health care provider (74). Adherence to ASMs is key to treatment success, and one of the main causes of treatment failure and seizure recurrence for epilepsy is poor adherence to prescribed medications (75).

Adherence to ASMs in children with epilepsy is variable. Previous studies have reported nonadherence in 30% to 70% of children (76–78). The relationship between seizure control and adherence to treatment is well documented. Studies have shown that missing a single dose of ASM may cause seizure recurrence (79). Modi et al also demonstrated that adherence trajectories can explain a proportion of the variability in longitudinal seizure outcomes, and can predict seizure outcome in pediatric patients (80).

Previous studies have documented multiple factors affecting adherence to ASMs in pediatric patients. These include patient age, seizure types, seizure frequency, duration of epilepsy, presence of other comorbidities, polytherapy, having side effects to ASMs or fear of side effects, non-availability of ASMs, forgetfulness, financial constraints, and caregivers' knowledge (81–85).

Adherence may be more compromised in low resource countries like Lebanon, where new barriers to treatment arise like high health care costs in the absence of reimbursement, in addition to unavailability of a wide range of drugs. An assessment of adherence to ASM treatment and factors influencing it is therefore of great importance. This will allow establishment of interventions to increase adherence, and improve the management of pediatric epilepsy in Lebanon.

I.13. **Research Objectives and Aims**

In clinical practice, it is difficult to predict at the time of diagnosis which children will develop poor seizure control or become drug resistant, except for some syndromes with known prognosis. For example, self-limited focal epilepsies are known to have an excellent age-dependent prognosis, while other syndrome such as the developmental and epileptic encephalopathies are known to have a much poorer outcome (13). Identification of a syndrome however can't be achieved early on after diagnosis, as it requires a detailed clinical history and sometimes multiple EEG recordings (13). It is therefore necessary to identify baseline clinical factors predictive of outcome regardless of the syndrome diagnosis.

A major consideration to be taken while assessing factors predictive of seizure outcome is the study directionality. Multiple retrospective studies have been conducted in the past, but these studies are dented by recruitment bias as they tend to not include patients with milder forms of epilepsy (86). Also a causal relationship between the variables and the outcome can't be definitively established. Prospective studies that identify all patients with new onset epilepsy in a defined population over a fixed period of time and follow them up will have the least recruitment bias and yield better results (86).

This aim of this project is to evaluate treatment outcome and psychiatric disorders in newly diagnosed children with epilepsy.

Aim 1: Identify early predictors of seizure remission based on baseline clinical characteristics, initial EEG, and brain MRI findings in large cohort of children with in newly diagnosed children.

Aim 2: Identify predictors of drug resistant epilepsy in different childhood epilepsy syndromes.

Aim 3: Evaluate the prevalence of psychiatric disorders and associated factors in children with epilepsy in Lebanon.

Figure 1 provides an overview of the conceptual framework used in this project. To evaluate treatment outcome, we selected two dependent variables as markers of treatment outcome: two-year remission (defined as any period of two-year seizure freedom on treatment), and drug resistance (defined as failure of two appropriately chosen ASM schedules). The literature has reported on many variables that are associated with remission, however for this study we wanted to identify early predictive factors that are available at baseline visit and to develop a decision tree to identify children at risk of poor seizure control. Among the independent variables used to build this model

were age at epilepsy onset, initial EEG results, brain MRI findings, presence and severity of intellectual and developmental delay, and pretreatment number of seizures and types. To evaluate predictors of drug resistance, we wanted to conduct this analysis after stratifying children according to their epilepsy syndrome, and to conduct a subgroup analysis for each type of epilepsy, because we hypothesized that the predictors of drug resistance would vary across different syndrome groups due to differences in their clinical characteristics. Among the independent variables included in this analysis were age at epilepsy onset, EEG results, brain MRI findings, presence and severity of intellectual and developmental delay, psychiatric comorbidities, number of seizure types, number of seizures, and types of seizures. Furthermore, since management of epilepsy doesn't only comprise seizure control but also targeting epilepsy comorbidities, we wanted to evaluate the frequency of psychiatric comorbidity in children with epilepsy residing in Lebanon, since this topic had not been previously explored in the region and we expected that these comorbidities were underdiagnosed and undertreated. We did a medical record review of all the data accumulated over the duration of follow-up for each child to look for any diagnosis of a psychiatric disorder. We also evaluated the associations between psychiatric disorders and different clinical variables such as seizure control.

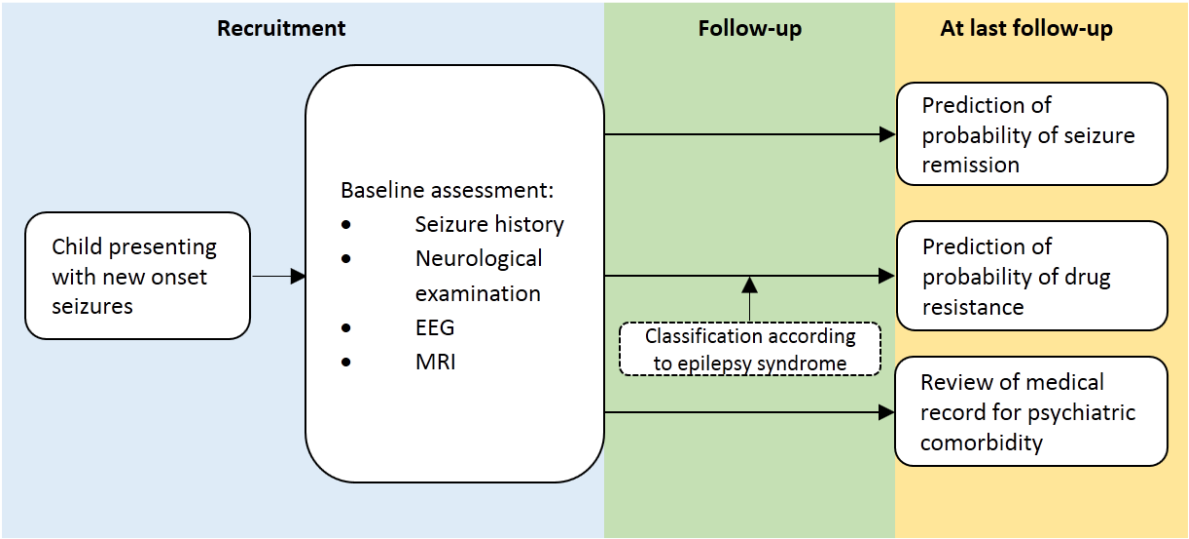


Figure 1 Conceptual framework of the study.

Chapter II. Project context

II.1. **Background on Lebanon**

This project is conducted in the Republic of Lebanon, a state located in the Near East. It is a country of 10452 sq. km. on the Mediterranean Sea, located at the intersection of three continents: Europe, Asia and Africa.

As of 2021, the United Nations Department of Economic and Social Affairs (UNDESA) Population Division estimated the population of Lebanon to be 5.6 million (87). Children and young people (aged 0–24 years) are estimated to constitute 42 % of the total population (87).

Lebanon is divided into 9 governorates with the following population distribution: Akkar (7.8%), Beqaa (9.9%), Nabatieh (7.1%), Baalbek-Hermel (8.5%), Beirut (7.9%), Mount Lebanon (28.1%), South Lebanon (10.9%), North Lebanon (14.6%), Keserwan-Jbeil (5.2%) (figure) (88).

Figure 1 Administrative governorates of Lebanon

II.2. **The Lebanese Health System**

The health delivery system is in general curative-oriented and technology-driven, except for Primary Health Care which are community-based services oriented towards promotion and prevention.

II.2.1. Hospital care

The hospital network is comprised of 165 public and private institutions distributed on all the Lebanese territory and covering all medical and surgical specializations (89).

The public hospitals, which provide free general care, are in general under-equipped which leads to suboptimal quality services. Today, there are 29 public hospitals (one of which has a university hospital status) representing a total of 2700 bed.

The private hospital sector is the main component and backbone of the Lebanese healthcare system. Highly developed both in number and capacity, it includes 136 long and short stay hospitals, with a total of 12648 beds (Private Hospitals Syndicate, 2009) which account for 82% of the country's total capacity. They are mainly general multidisciplinary hospitals with 80 to 400 beds per hospital. Twelve of these hospitals have the status of university hospitals.

II.2.2. Ambulatory care

Outpatient care is provided by a multitude of primary healthcare facilities ranging from physicians in solo practice to multidisciplinary polyclinics. The country has 282 primary healthcare providing a wide range of medical services (89). High technology is also invading some outpatient facilities, including medical laboratories, radiology and other non-invasive diagnostic centers, physiotherapy and dental care clinics. The quality of services varies by region and provider.

A big number of dispensaries, belonging to Non-Governmental Organizations and political forces, are also licensed filling the gap caused by the deficiency in the public sector.

II.2.3. Health insurance coverage

According to the 2018-2019 Labor Force and Households Living Conditions Survey of Lebanon (90), only 55.6% of the Lebanese population were covered by at least one type of health insurance. This proportion has improved since 2004, when it was only 44.9%, mainly due to health programs for refugees and displaced persons, which cover non-Lebanese residents. Yet, an estimated 44.4% of Lebanon's residents remain without any

form of health coverage as of 2018–2019. Concerning the elderly population (65 years and above), it is estimated that around 33.6 % were not benefiting from any type of coverage.

The main sources of health insurance coverage in Lebanon were: The National Social Security Fund (NSSF) (45.5% of beneficiaries), army and the internal security forces (20.1%), UNHCR or other organizations (11.5%), private insurance (10.5%), Civil Servants Cooperation (5.9%), mutual fund through an institution or union (4.8%), or other sources (3.8%).

II.3. **Methodological aspects of the project**

The aim of this research was to longitudinally identify clinical characteristics predictive of treatment outcome in children with new-onset seizures initiated on ASM treatment. A second objective was to assess the prevalence of psychiatric disorders and associated factors in these children. This was a multicenter prospective study with centralized monitoring at the American University of Beirut Medical Center (AUBMC). This project began in 2010 and is a collective contribution from different hospitals and neurology centers in different regions in Lebanon that are attended by most children with epilepsy (AUBMC, Saint George Hospital Medical University Center, Hotel Dieu de France Hospital...), with the aim of including a larger sample size with more generalizable findings. Pediatric neurologists from different centers in Lebanon have been referring patients with new onset seizures to AUBMC since 2010, where the study objective is explained, written parental consent is obtained, and a full work-up is performed. Up till today, around 4000 children with new onset seizures have been recruited and are being followed up.

The workup performed at AUBMC at initial presentation includes a detailed history and a thorough description of the seizures obtained from the patient and an eyewitness, complete physical and neurological examinations, a 3-hour sleep deprived video- EEG recording interpreted by two experienced epileptologists, and an epilepsy protocol brain MRI interpreted by a neuroradiologist. Specific methodologies for obtaining and interpreting EEG and brain MRI findings are detailed in each study in subsequent chapters. Ethical approval for this study was obtained from the Institutional Review Board of the AUBMC. Patients are then evaluated by telephone consultations and follow-up visits with repeat EEGs as clinically indicated. At each follow-up visit or phone call, information about seizure frequency, changes in ASM therapy or posology, adverse events and adherence to treatment are systematically recorded. All data collected were reviewed by the prinicipal researcher and by an epileptologist before data analysis, to make sure the correct syndrome and seizure classification was made.

Chapter III. Early predictors of remission in children and adolescents with new-onset epilepsy: A prospective study

III.1. **Background**

The ultimate goal in the management of epilepsy is the complete resolution of seizures and the discontinuation of medications. While epilepsy can't be definitively cured, since relapse rates for epileptic patients will probably always remain higher than the general population, the ILAE considers that epilepsy can be "resolved". Resolved epilepsy refers to patients who had an age-dependent epilepsy syndrome and are now past the applicable age, or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years. A marker of seizure prognosis that has been used throughout the literature is seizure remission. Remission is a relative concept and its definition has varied among studies, from 2-year seizure freedom at any time, to 1-year seizure freedom at last contact, to 5-years of seizure freedom with the last two years off medication.

In clinical practice, an important marker of prognosis is achieving 2-year remission, since drug discontinuation may be considered in some children after a minimum of two years of seizure freedom. This goal appears realizable with the introduction of multiple ASMs throughout the past decade. However, studies have shown that one third of children fail to achieve seizure control. For this study, we wanted to evaluate clinical variables available at baseline; at first clinic visit when a diagnosis of epilepsy was made; that could predict the likelihood of achieving seizure remission, defined as having two years of complete seizure freedom on treatment. This study was a large scale prospective study with children recruited at the time of epilepsy onset and initiation of treatment.

Article Published in Seizure: European Journal of Epilepsy
(Appendix 7)

III.2. **Abstract**

Purpose: This study aims to identify predictive factors of a two-year remission (2YR) in a cohort of children and adolescents with new-onset seizures based on baseline clinical characteristics, initial EEG and brain MRI findings.

Methods: A prospective cohort of 688 patients with new onset seizures, initiated on treatment with antiseizure medication was evaluated. 2YR was defined as achieving at least two years of seizure freedom during the follow-up period. Multivariable analysis was performed and recursive partition analysis was utilized to develop a decision tree.

Results: The median age at seizure onset was 6.7 years, and the median follow-up was 7.4 years. 548 (79.7%) patients achieved a 2YR during the follow up period. Multivariable analysis found that presence and degree of intellectual and developmental delay (IDD), epileptogenic lesion on brain MRI and a higher number of pretreatment seizures were significantly associated with a lower probability of achieving a 2YR. Recursive partition analysis showed that the absence of IDD was the most important predictor of remission. An epileptogenic lesion was a significant predictor of non-remission only in patients without evidence of IDD, and a high number of pretreatment seizures was a predictive factor in children without IDD and in the absence of an epileptogenic lesion.

Conclusion: Our results indicate that it is possible to identify patients at risk of not achieving a 2YR based on variables obtained at the initial evaluation. This could allow for a timely selection of patients who require close follow-up, consideration for neurosurgical intervention, or investigational treatments trials.

Keywords: Children and adolescents, new-onset seizures, remission, epileptogenic lesion, intellectual and developmental delay, number of pretreatment seizures

III.3. **Introduction**

It is well established that despite the availability of numerous novel antiseizure medications (ASMs), one third of children with new-onset seizures will not achieve seizure remission (1–3). These children endure the physical, psychological and social consequences of intractable seizures and face an elevated risk of death (4,5). Despite its clinical importance, the early prediction of treatment outcome remains a major challenge (6), with only a limited number of large, community-based, long-term studies evaluating early predictors of medical refractoriness in childhood epilepsy (7–9). Certain childhood electroclinical syndromes, such as the self-limited focal epilepsy with centrotemporal spikes (SLECTS) are known to have an excellent prognosis, while others, such as the Lennox-Gastaut syndrome, are associated with a much poorer outlook (10,11). Although the determination of a specific electroclinical syndrome could provide guidance on management and clarify long-term prospects, syndromic diagnosis is frequently difficult to ascertain at the time of seizure onset (11). An alternative approach is to develop a model that can predict treatment outcome based on variables obtained near the time of the initial evaluation. This would enable earlier consideration of surgical intervention or alternative nonmedicinal treatments for children at high risk of not achieving seizure remission while avoiding the burden of ineffective polytherapy trials (12).

This prospective study aims to identify the prognostic variables for a two-year remission (2YR) following initiation of treatment with an ASM in children and adolescents with new-onset seizures, solely based on the clinical characteristics, EEG and brain MRI findings obtained at the time of the initial visit. A secondary objective is to calculate remission rates when stratified according to the latest International League Against Epilepsy (ILAE) classification of the epilepsies (11,13).

III.4. **Materials and Methods**

III.4.1. Study Design

A cohort of children and adolescents with new-onset seizures was identified from an ongoing centralized prospective study conducted at the American University of Beirut Medical Center (AUBMC) in association with the Lebanese Chapter of the International League against Epilepsy (ILAE). Although an official census is not available, it is estimated that the Lebanese population consists of 5.3 million individuals residing in the six governorates (14), with approximately 31% of the population being 17 years of age or younger (15). This research study is a multicenter collaborative effort involving numerous neurologists distributed across the six governorates. These neurologists refer their patients with newly diagnosed seizures to the AUBMC, where a full clinical evaluation and extensive workup are performed.

As per protocol, the work-up included a detailed history and a thorough description of the events obtained from the patient and an eyewitness, complete physical and neurological examinations, a 3-hour sleep deprived video-EEG recording interpreted by experienced epileptologists, along with an epilepsy protocol brain MRI interpreted by a neuroradiologist with vast experience in the neuroimaging of patients with epilepsy. Patients were subsequently evaluated by telephone consultations and yearly follow-up visits with repeat EEGs as clinically indicated. More frequent follow-up visits were scheduled in case of seizure recurrence or adverse events related to ASM. At each follow-up visit or phone call, information about seizure frequency, changes in drug therapy or posology, adverse events and adherence to treatment were systematically recorded. Adherence to treatment was monitored through inquiries made to the caregiver/patient regarding the administration of ASM as prescribed. For children receiving valproate, carbamazepine, phenytoin or phenobarbital, routine monitoring of serum levels for these medications was conducted. However, due to the unavailability of local facilities for checking serum levels of newer ASMs and the high associated costs involved, which were not affordable for most patients or their parents, the serum levels of these drugs were rarely monitored.

III.4.2. Inclusion/exclusion criteria

For this study, we enrolled consecutive children ranging from 6 months to 18 years of age who presented with one or more unprovoked seizure between March 2010 and May 2016, and who were initiated on treatment with an ASM at the time of recruitment and had a follow-up of at least two years. Patients who presented with acute symptomatic or febrile seizures, as well as those with a history of functional seizures, alcohol or drug

abuse, were excluded. Additionally, children with a follow-up period of less than two years while on ASM treatment and those non-compliant to their prescribed treatment regimen, were excluded. Patients who died or underwent surgery after enrollment were censored at the time of death or surgery.

III.4.3. Ethical approval and patient consent

This study was approved by the Institutional Review Board of the AUBMC, and all patients enrolled in this study had an informed consent signed by one of their parents.

III.4.4. Brain MRI and classification of neuro-imaging findings

Brain MRIs were obtained from a 1.5 or 3T scanner (Ingenia; Phillips Healthcare) using an imaging-acquisition protocol that included 3D T1 (1 mm slice thickness) and 3D fast fluid-attenuated inversion recovery (FLAIR; 0.9- or 1-mm slice thickness) of the whole brain with multiplanar reconstruction, axial and coronal inversion recovery (2 mm slice thickness), axial T2 TSE and T2 FFE (4 mm slide thickness) and axial diffusion weighted images (4-5 mm slice thickness). The 3D images were obtained with no interslice gap.

MRI findings were classified as epileptogenic or non-epileptogenic based on previously published criteria (16–18). MRI abnormalities consisting of isolated subcortical lesions or abnormal signal, nonspecific white matter hyperintensities, hydrocephalus, and brain atrophy were considered incidental findings.

III.4.5. Sleep deprived Electroencephalogram (EEG) and classification of EEG findings

The EEGs were recorded on digital Nicolet machines (Natus^{R} Neurodiagnostics) with electrodes placed according to the International 10-20 system. At the initial visit, a 3-hour sleep deprived video-EEG with sleep recording was recorded from all patients. At each follow-up visit, a 60-minute sleep deprived EEG recording was performed. The EEG obtained at the initial visit were stratified according to the presence or absence of interictal epileptiform discharges (IEDs). Focal IEDs were classified based on their topography, morphology and presence or absence of focal slowing into focal maturational or focal non-maturational discharges (19). The generalized spike wave discharges (GSWD) of the type seen in patients with a genetic generalized epilepsy (frequency of more than 2.5 Hz associated with a normal background) were labeled as idiopathic generalized discharges (19). The GSWD of the type seen in patients with a developmental and epileptic encephalopathy (frequency of less than 2.5 Hz associated with a slow and disorganized

background with or without concomitant focal or multifocal IEDs) were labelled as symptomatic generalized discharges.

III.4.6. Assessment of Intellectual and Developmental Delay

All patients underwent an assessment to evaluate for the presence and severity of intellectual and developmental delay (IDD). Children younger than 6 years of age were evaluated using the Denver Development Screening Test (20). Older children were assessed according to the Diagnostic and Statistical Manual of Mental Disorders criteria, which classifies intellectual delay as mild, moderate, severe, or profound based on deficits in intellectual functioning as well as difficulties in conceptual, social, and practical areas of living (21). For example, children with mild intellectual delay may struggle with learning abilities and exhibit immaturity in social interactions, with communication and language skills that are more concrete than expected for their age. Children with moderate intellectual delay display marked limitations compared to their peers, with significant differences in social and communicative behavior. However, children with mild and moderate intellectual delay can still care for their personal needs, including eating, dressing and hygiene. Children with severe and profound intellectual delay have limited or very limited language development and have substantial limitations in the conceptual domains. They require support or are completely dependent on others for all activities of daily living (21). For the purpose of our analysis, we combined children with severe and profound delays into a single category, and included three groups of IDD (mild, moderate, or severe). To ensure the accuracy and consistency of the assessments, research fellows with specialized training in administering these tests were responsible for conducting the evaluation and scoring the degree of deficit. These chosen assessment tools were selected based on factors such as feasibility in terms of cost, accessibility, time requirements, and training considerations. Since our aim was to identify predictors of seizure remission based on baseline clinical variables, the IDD severity score determined during the initial visit was used for the analyses.

III.4.7. Seizure types and determination of the electroclinical syndrome

Seizure types were classified according to the latest ILAE 2017 classification of seizure types (22). To ensure that the correct diagnosis of the epilepsy syndrome was made, the case report file of each child was entirely reviewed. The electroclinical syndromes were classified according to the latest International League Against Epilepsy (ILAE) classification of the epilepsies (11,13) with children stratified into one of five categories: (1) self-limited focal epilepsy, (2) genetic generalized epilepsy, (3) non-structural focal epilepsy, (4) structural focal epilepsy, (5) developmental and epileptic encephalopathy.

III.4.8. Outcome

A 2YR was defined as achieving at least two consecutive years of complete seizure freedom at any time during the entire follow-up period. Time to initial 2YR was defined as the elapsed time between treatment initiation and the time when a two-year seizure freedom was attained.

III.4.9. Variables

The following variables were collected for each patient at the time of enrollment in the study: (1) demographics; (2) disease characteristics (age at seizure onset, seizure types at onset, number of seizure types at onset, pretreatment number of seizures, time of seizure occurrence); (3) epilepsy risk factors (number of risk factors, family history of epilepsy, parental consanguinity, perinatal insult, febrile seizures, head trauma, CNS infection); (4) IDD (presence and severity); (5) IED types on initial EEG; (6) Brain MRI results (presence or absence of epileptogenic lesion).

III.4.10. Statistical Analysis

Descriptive results were reported for the demographic and clinical characteristics. The cumulative time-dependent probability of 2YR was calculated using Kaplan-Meier survival tables and curves. Cox proportional hazards model was used to identify variables associated with 2YR. Assumptions of proportional hazards was tested using Log-Log. Variables yielding p-values < 0.2 in univariable analysis were tested in a multivariable analysis with significance level set at 0.05. Data were presented as hazard ratios (HR) and adjusted HR with 95% confidence intervals (CI).

In addition, a recursive partition analysis was performed to identify variables associated with higher or lower probabilities of achieving a 2YR. For this analysis, we used the Chi-square Automatic Interaction Detector with cross-validation. At each step, the Chi-square Automatic Interaction Detector algorithm chooses the independent variable that has the strongest interaction with the dependent variable using P values with a Bonferroni correction as splitting criteria. The final result is a decision tree with various nodes that can be used to predict the probability of achieving a 2YR in each subgroup. Statistical significance was set at the 5% level. All statistical analyses were performed using SPSS, version 23.

III.5. **Results**

Of the 827 enrolled children, 139 were excluded for the following reasons: 72 were lost to follow-up or had a follow-up of less than two years and 67 were poorly compliant or received ASM for less than two years. This left 688 children who met the inclusion/exclusion criteria and who were included in the analyses (Figure 1). The distribution of patients included in this study closely mirrored the geographical distribution of the population across Lebanon's six administrative governorates. Specifically, within our study cohort, 16% of the children resided in the Beirut governorate, 32% in Mount Lebanon, 23% in North Lebanon, 13% in the Bekaa, and 16% in South Lebanon and Nabatieh.

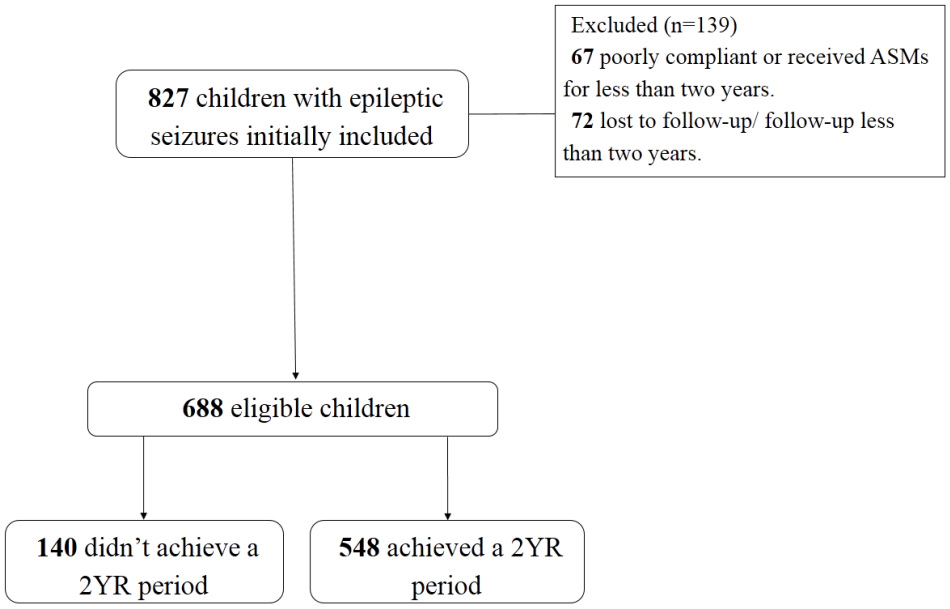


Figure 1 Flow chart of the study cohort. 2YR: 2-year remission, ASMs: antiseizure medications.

III.5.1. Demographic characteristics and epilepsy risk factors

The demographic characteristics and epilepsy risk factors of the study population are summarized in Table 1a. More than half of the children were males (59.2%) and 181 (26.3%) had IDD. The median age at time of seizure onset was 6.7 years (IQR 2.3-11.0 years) and the median follow-up was 7.4 years (IQR 5.9-9.0 years) with a range from 2.0-11.6 years. Risk factors for epilepsy were present in 459 children (66.7%) and included 208 children (30.2%) with a family history of epilepsy, 109 children (15.8%) born from consanguineous marriage, and 112 children (16.3%) with a history of perinatal insult.

Table 1a. Demographic characteristics and epilepsy risk factors of the study population

Variable	Mean (STD)	Range	Median (IQR)
Age at seizure onset (years)	7.0±5.0	0.5-17.6	6.7 (2.3-11.0)
Duration of follow-up (years)	7.2±2.3	2.0-11.6	7.4 (5.9-9.0)
Variable		**N (%)**	
Gender			
Male		407 (59.2)	
Female		281 (40.8)	
Age at seizure onset			
0.5 <2 yrs		157 (22.8)	
2-<5 yrs		116 (16.9)	
5-<12 yrs		272 (39.5)	
12-<18 yrs		143 (20.8)	
Intellectual and developmental delay			
None		507 (73.7)	
Mild		58 (8.4)	
Moderate		52 (7.6)	
Severe		71 (10.3)	
Presence of epilepsy risk factors			
Yes		459 (66.7)	
Number of epilepsy risk factors			
None		229 (33.3)	
1		266 (38.7)	
2		159 (23.1)	
≥3		34 (4.9)	
Type of epilepsy risk factor			
Family history of epilepsy		208 (30.2)	
Consanguinity		109 (15.8)	
Perinatal insult		112 (16.3)	
Febrile seizures		85 (12.4)	
Head trauma		36 (5.2)	
CNS infection		15 (2.2)	

STD: standard deviation; IQR: interquartile range; CNS: central nervous system

III.5.2. Clinical characteristics

The clinical characteristics of the study population are summarized in Table 1b. The majority of patients (77.8%) experienced a single seizure type at the time of their initial evaluation. The most common seizure type was focal impaired awareness seizures (FIAS) which occurred in 267 children (38.8%). This was followed by focal to bilateral tonic-clonic seizures (FBTC) in 138 children (20.1%), focal aware seizures in 83 children (12.1%) and generalized onset tonic-clonic seizures (GOTC) in 72 children (10.5%). Prior to treatment initiation, 350 children (50.9%) experienced between one and five seizures, while 233 children (33.9%) experienced more than 100 seizures. This typically was the case in children who experienced frequent daily absence seizures (n=82), myoclonic seizures (n=55), or epileptic spasms (n=67). A small percentage (19.2%) experienced both nocturnal and diurnal seizures.

IEDs were observed on the initial EEG of 487 children (70.8%). GSWD of the idiopathic type and focal non-maturational discharges occurred more frequently (23.8% and 24.0% respectively) than GSWD of the symptomatic type and focal maturational discharges (12.4% and 12.1% respectively). An epileptogenic lesion was present on the brain MRI of 191 (27.8%) children, with MCD identified in 61 (31.9%) and hypoxic injury in 46 (24.1%). Out of the 191 patients with epileptogenic lesions detected on brain MRI, 140 exhibited epileptiform discharges that lateralized to the side of the lesions. Among the remaining 51 patients, 35 displayed no interictal discharges on EEG, and 16 patients exhibited discordant or multifocal epileptiform discharges. In cases where no associated epileptiform discharges were present, the brain lesion was considered likely epileptogenic, as the seizure semiology was concordant with the location of the brain lesion. Of the 10 patients with discordant epileptiform discharges, 6 showed hypsarrhythmia on their EEG recordings.

Table 1b. Clinical characteristics of the study population

Seizure types at presentation [a]	
Focal onset	
Focal impaired awareness seizures	267 (38.8)
Focal aware seizures	83 (12.1)
Focal to bilateral tonic-clonic seizures	138 (20.1)
Generalized onset seizures	
Generalized onset tonic-clonic seizures [b]	72 (10.5)
Absence seizures	82 (11.9)
Myoclonic jerks	55 (8.0)
Epileptic Spasms	67 (9.7)
Other[c]	32 (4.7)
Unknown onset	
Unknown-onset tonic clonic seizures	69 (10.0)
Pretreatment number of seizures	
1-5	350 (50.9)
6-10	42 (6.1)
11-100	63 (9.2)
>100	233 (33.9)
Number of seizure types at presentation	
1	535 (77.8)
2	127 (18.5)
≥3	26 (3.8)
Time of seizure occurrence	
Nocturnal	162 (23.5)
Diurnal	394 (57.3)
Mixed	132 (19.2)
IED on EEG	
No	201 (29.2)
Yes	487 (70.8)
IED type on EEG	
Focal	
Maturational	83 (12.1)
Non-maturational[d]	165 (24.0)
Generalized	
Idiopathic[d]	164 (23.8)
Symptomatic	85 (12.4)
Epileptogenic lesion on MRI*	
Yes	191 (27.8)
No	489 (71.1)
Type of Epileptogenic lesion	
Malformations of cortical development	61 (31.9)
Periventricular leukamalacia/hypoxia	46 (24.1)
Vascular	31 (16.2)
Mesial temporal sclerosis	15 (7.9)
Neurocutaneous syndromes	13 (6.8)
Other[e]	25 (13.1)

IED: interictal epileptiform discharges; EEG: electroencephalogram; MRI: magnetic resonance imaging.
[a] Total percentage above 100% because some children experienced more than one seizure type at presentation.
[b] Generalized tonic-clonic seizures were considered of generalized onset if the child had definite absence seizures or myoclonus, or if the event was witnessed from onset with no signs of focality.
[c] Other seizure types include tonic seizures in 13 children (1.9%), eyelid myoclonia in 9 children (1.3%), drop attacks in 8 children (1.2%) and myoclonic absence and myoclonic-atonic seizures in one child each (0.1%).
[d] 10 children were diagnosed with photosensitive occipital lobe epilepsy and had both focal and idiopathic generalized epileptiform discharges
* A brain MRI was not performed on 8 children.
[e] Other lesions consisted of post-infectious encephalomalacia with cortical gliosis in 7 (3.7%), metabolic disorders and post-traumatic encephalomalacia and gliosis in 5 children each (2.6%), tumors in 5 children (2.2%) and leukodystrophy in 3 (1.5%).

III.5.3. Treatment characteristics

During the follow-up period, 322 children (46.8%) were prescribed only one ASM, while 187 children (27.2%) received two ASMs, either as monotherapy or in combination. The number of ASMs prescribed ranged from 1 to 10 with a median of two drugs. The patients were treated with an ASM for a mean duration of 4.0 ±1.8 years (range: 2.0-10.5 years). The most frequently prescribed ASM was valproate (73.4%), followed by levetiracetam (32.1%). Nonpharmacological treatments were received by 51 children (7.4%), that included 23 who underwent epilepsy surgery, 29 inserted with a vagus nerve stimulator, and two treated with the ketogenic diet.

III.5.4. Remission rates

To date, 548 children (79.7%) have achieved a 2YR. The median time to achieve a 2YR was 2.1 years (95% CI: 2.0-2.1), with a range of 2.0 to 9.7 years. The cumulative probabilities of achieving a 2YR were 43.1% (95% CI: 39.4-46.8%) at 24 months, 69.3% (95% CI: 65.9-72.9%) at 36 months, 75.5% (95% CI: 72.1-78.8%) at 48 months, 81.7% (95% CI: 78.6-84.8%) at 72 months, and 86.6% (95% CI: 83.3-90.0%) at 120 months after treatment initiation (Figure 2).

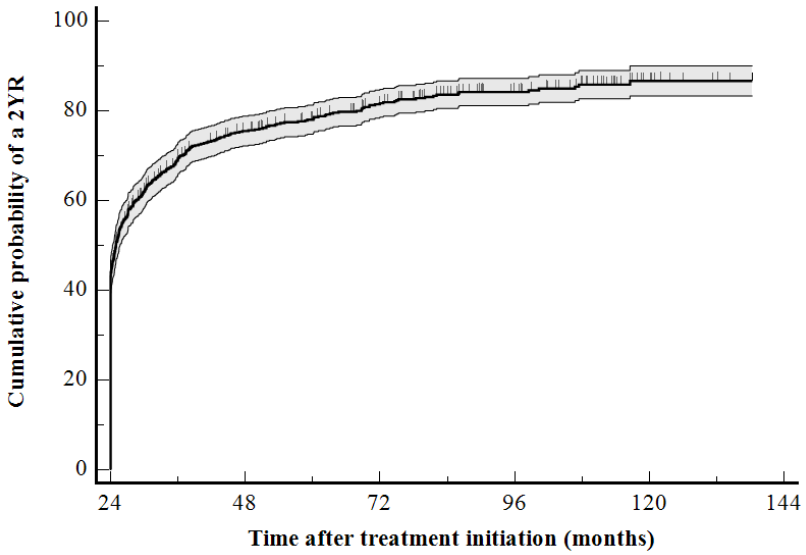


Figure 2 Figure 2 Kaplan-Meier Curve: Cumulative probability of achieving a two-year remission (2YR) following treatment initiation. Dashed lines represent censored data. Grey shade represents 95% confidence interval.

III.5.5. Determinants of remission

III.5.5.1. Univariable analysis

Univariable analysis showed that several factors were associated with a lower probability of remission. These included a younger age at seizure onset, a greater number of pretreatment seizures, experiencing three or more types of seizures at onset, the presence and degree of IDD, the presence of an epileptogenic lesion on MRI, mixed time of seizure occurrence (both nocturnal and diurnal), a history of perinatal insult, parental consanguinity, and the presence of focal non-maturational or generalized discharges of the symptomatic type (Table 2).

III.5.5.2. Multivariable analysis

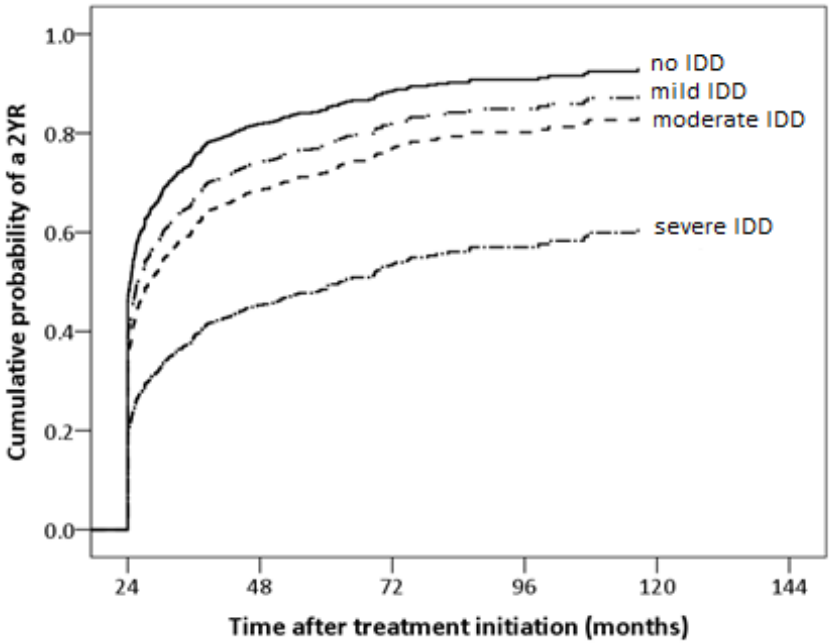
In multivariable analysis (Table 2), factors that independently predicted a lower probability of remission were a greater number of seizures prior to treatment initiation, the presence and severity of IDD and the presence of an epileptogenic lesion on MRI.

Children who experienced more than 100 seizures prior to treatment initiation with an ASM had a lower probability of achieving a 2YR compared to those who experienced up to five seizures (HR= 0.7, 95% CI: 0.5-0.9, p= 0.011). This probability was further reduced for children with a history of 11-100 seizures prior to treatment (HR= 0.6, 95% CI 0.4-0.8, p= 0.002). The probability of achieving a 2YR varied depending on the presence and severity of IDD. While no significant difference was found between children with mild or moderate IDD and those with no IDD, the probability of achieving a 2YR was significantly lower in children with severe IDD (HR= 0.4, 95% CI 0.2-0.6, p< 0.001) (Supplementary Figure 1). Finally, the presence of an epileptogenic lesion on brain MRI significantly reduced the probability of achieving a 2YR (HR=0.6, 95% CI 0.5-0.8, p< 0.001) (Supplementary Figure 2).

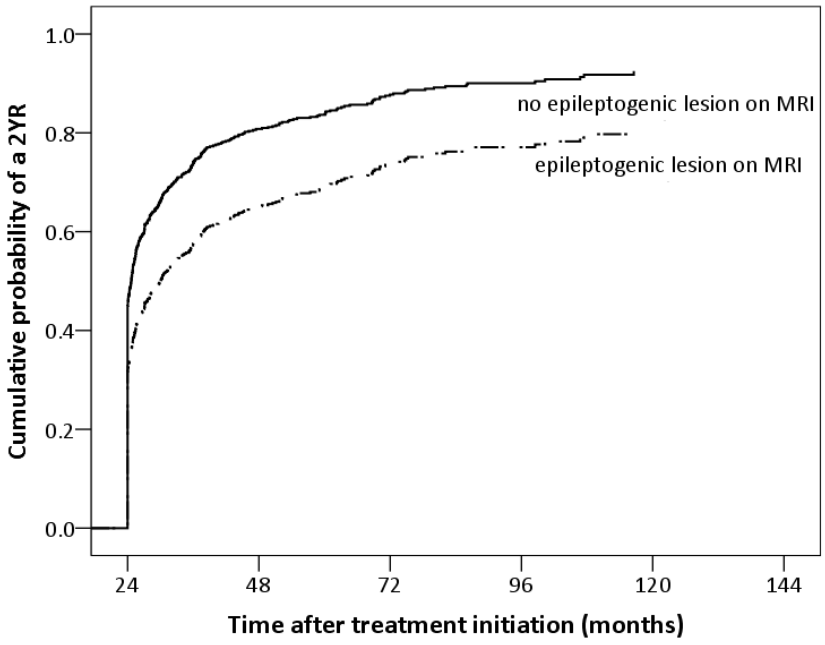
Table 2 Univariable and multivariable Cox regression results for two-year remission by clinical characteristics, EEG and brain MRI obtained at the initial visit.

	Unadjusted HR			Adjusted HR		
Comparison	**HR**	**95%CI**	**p-value**	**HR**	**95%CI**	**p-value**
Pretreatment number of seizures						
1-5	1		-	1		-
6-10	0.92	0.65-1.29	0.612	0.82	0.57-1.18	0.284
11-100	0.53	0.38-0.74	**<0.001**	0.58	0.41-0.82	**0.002**
>100	0.63	0.52-0.77	**<0.001**	0.70	0.53-0.92	**0.011**
Intellectual and developmental delay						
None	1		**-**	1		**-**
Mild	0.65	0.48-0.89	**0.007**	0.79	0.56-1.12	0.181
Moderate	0.49	0.34-0.71	**<0.001**	0.68	0.44-1.03	0.072
Severe	0.25	0.17-0.37	**<0.001**	0.35	0.21-0.59	**<0.001**
Presence of epileptogenic lesion on MRI	0.47	0.38-0.58	**<0.001**	0.64	0.49-0.82	**<0.001**
Female vs. male	0.98	0.82-1.16	0.769			
Age at seizure onset						
0.5-<2 yrs	1		**-**	1		-
2-<5 yrs	1.44	1.08-1.91	**0.012**	0.95	0.69-1.30	0.759
5-<12 yrs	1.7	1.34-2.16	**<0.001**	1	0.76-1.35	0.903
12-<18 yrs	2.03	1.56-2.65	**<0.001**	1	0.73-1.38	0.962
Number of seizure types at onset						
1	1		**-**	1		**-**
2	0.91	0.73-1.13	0.385	1.01	0.8-1.27	0.986
≥3	0.41	0.23-0.7	**0.001**	0.56	0.3-1.03	0.062
Time of seizure occurrence						
Nocturnal	1		-			-
Diurnal	1.05	0.86-1.28	0.645	1.16	0.93-1.4	0.188
Mixed	0.67	0.51-0.87	**0.003**	0.96	0.71-1.31	0.830
Presence of epilepsy risk factors	0.91	0.76-1.08	0.304			
Number of epilepsy risk factors						
None				1		-
1	1		-	1.1	0.87-1.36	0.414
2	0.82	0.66-1.03	0.093	0.99	0.7-1.39	0.950
≥3	0.72	0.47-1.11	0.136	0.99	0.55-1.80	0.991
Perinatal insult	0.67	0.52-0.86	**0.002**	1.04	0.76-1.43	0.794
Febrile seizure	1.19	0.94-1.52	0.153	1.26	0.93-1.72	0.135
Head trauma	1.15	0.81-1.65	0.434			
CNS infection	0.7	0.37-1.31	0.26			
Parental consanguinity	0.73	0.6-0.9	**0.003**	0.85	0.64-1.12	0.241
Family history of epilepsy	1.05	0.89-1.24	0.579			
IED type on initial EEG						
No discharges	1		-	1		-
Focal maturational	1.23	0.95-1.61	0.118	1.05	0.78-1.42	0.747
Focal non-maturational	0.69	0.54-0.88	**0.002**	0.82	0.63-1.06	0.135
Generalized idiopathic	1.19	0.96-1.5	0.12	1.14	0.85-1.53	0.363
Generalized symptomatic	0.37	0.26-0.52	**<0.001**	1.09	0.66-1.77	0.742

Abbreviations: CI; confidence interval; HR: hazard ratio; CNS: central nervous system; IED: interictal epileptiform discharges; EEG: electroencephalogram; MRI: magnetic resonance imaging.



Supplementary figure 1 Cox proportional hazards cumulative 1-survival curves stratified according to presence and severity of IDD. 2YR: two-year remission. IDD: intellectual and developmental delay.



Supplementary figure 2 Cox proportional hazards cumulative 1-survival curves stratified according to presence or absence of epileptogenic lesion on brain MRI. 2YR: two-year remission; MRI: magnetic resonance imaging.

III.5.5.3. Recursive Partition Analysis

The recursive analysis identified those same variables that partitioned the patients into a decision tree with five groups (Figure 3). The first important predictor of failure to achieve remission was the presence and severity of IDD, which classified children into three groups: those with no IDD, those with mild or moderate IDD and those with severe IDD. 60% of children with severe IDD and 31.5% of children with mild or moderate IDD failed to achieve a 2YR compared to 10.6% of children with no IDD.

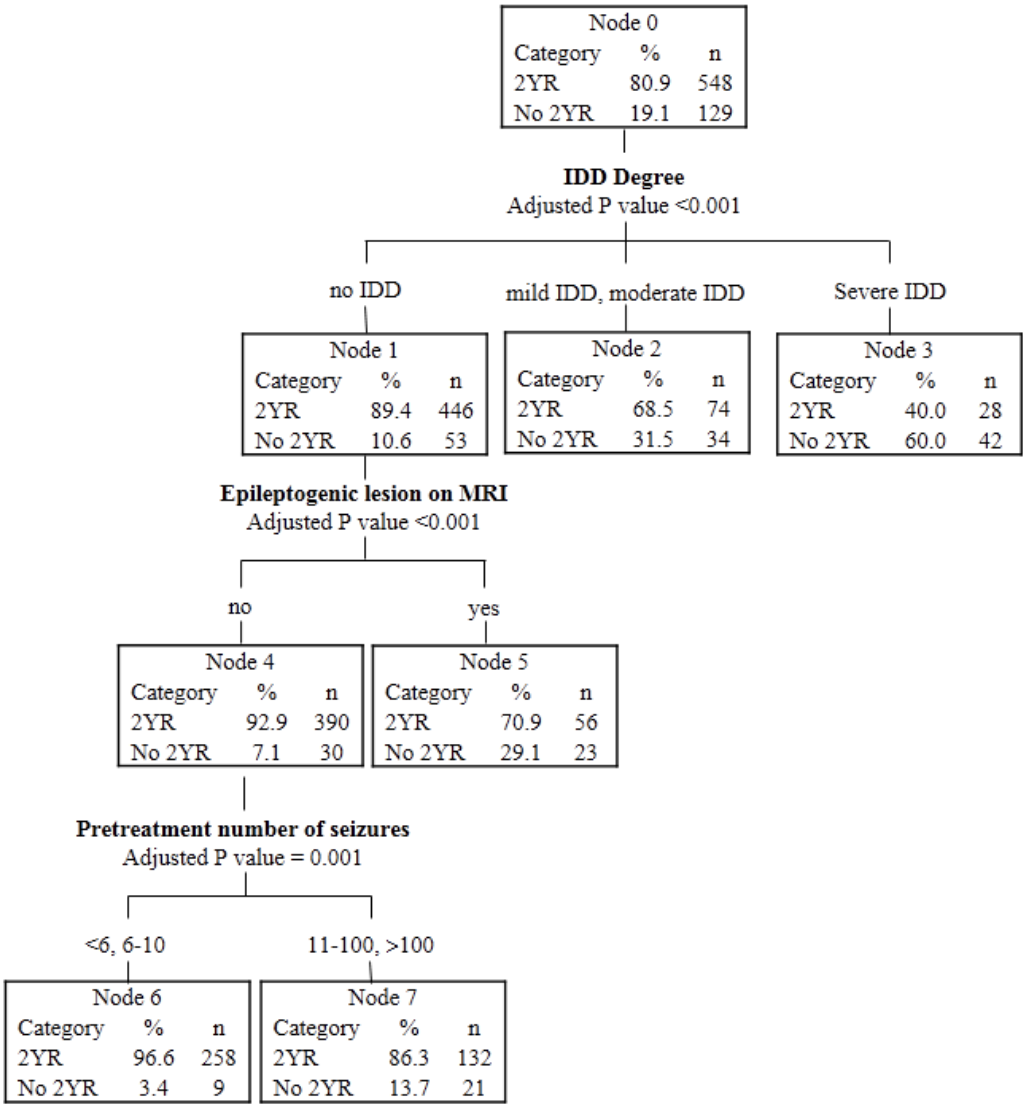


Figure 3 Recursive partition analysis stratified children into a decision tree with 5 groups based only on the presence and severity of IDD, presence of epileptogenic lesion on MRI, and pretreatment number of seizures. IDD: intellectual and developmental delay, MRI: magnetic resonance imaging, 2YR: two-year remission

The next predictor variable, the presence or absence of an epileptogenic lesion on brain MRI, only applied to children with no IDD where 29.1% of children with a lesion failed to achieve a 2YR compared to 7.1% of children with no lesion. Finally, the terminal predictor in children with no IDD and no epileptogenic lesion was the number of seizures prior to treatment initiation; 13.7% of children with more than 10 seizures prior to treatment initiation failed to achieve remission, compared to 3.4% in children with a lower number of seizures.

III.5.6. Remission rates stratified according to epilepsy syndromes

The majority of children in the study were diagnosed with focal epilepsy, with 121 children (17.6%) diagnosed with a self-limited focal epilepsy (SeLFE), 132 (19.2%) with a structural focal epilepsy and 186 (27.0%) with a non-structural focal epilepsy. 155 (22.5%) children were diagnosed with a genetic generalized epilepsy (GGE), while 94 (13.7%) were diagnosed with a developmental and epileptic encephalopathy (DEE). The associated 2YR rates for each syndrome are shown in Figure 4. The groups of children most likely to achieve a 2YR were those diagnosed with a SeLFE (97.5%), GGE (92.9%) and non-structural focal epilepsies (87.1%). In contrast, there was a lower likelihood of achieving a 2YR in children diagnosed with a structural focal epilepsy (59.8%) or DEE (47.9%). It is worth noting the variable distribution of epilepsy syndromes across different age groups. The highest prevalence of DEE was observed in children with seizure onset between 0 and 2 years (44.6%), while the lowest between 12 to 18 years (0.7%). Conversely, the lowest prevalence of GGE was in children with seizure onset between 0 and 2 years (4.5%), while the highest was in children with onset between 12 and 18 years (42.0%) (Supplementary Figure 3).

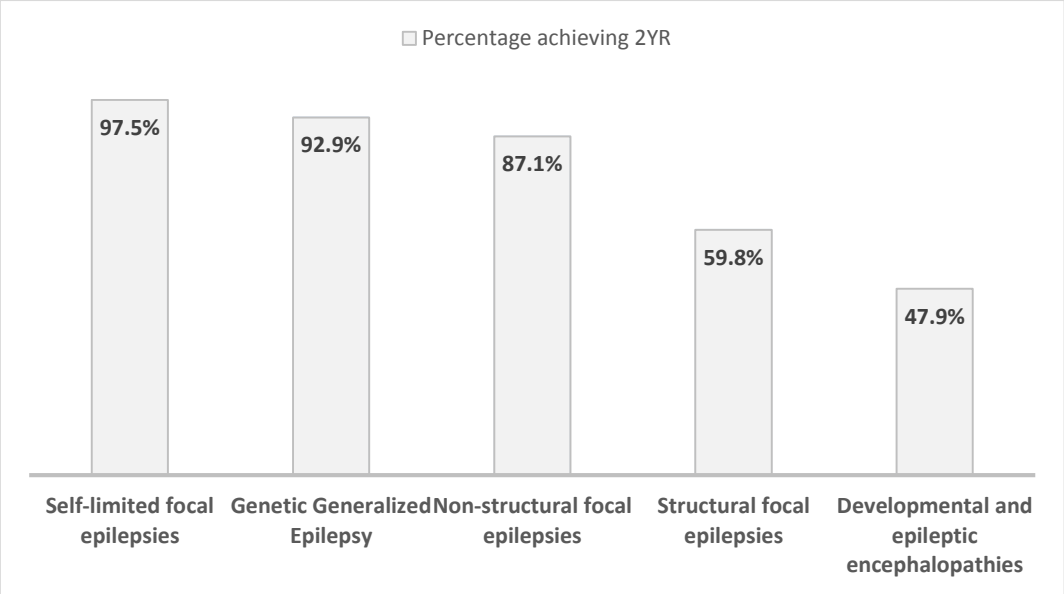
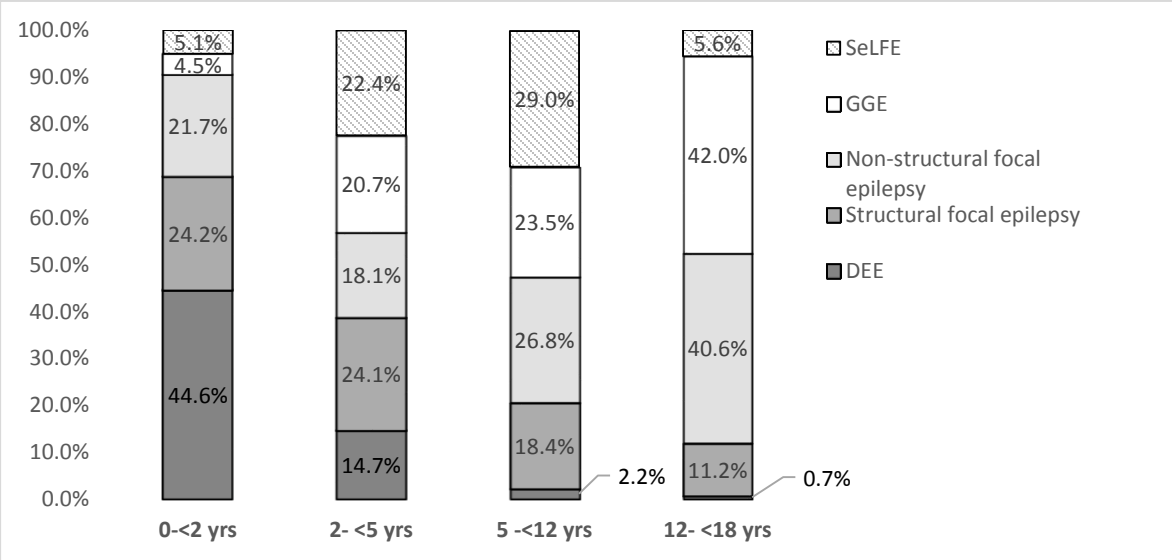


Figure 4 Percentages of children achieving a two-year remission (2YR) stratified according to the epilepsy syndromes.



Supplementary figure 3 Prevalence of epilepsy syndromes in each age group of epilepsy onset. SeLFE: self-limited focal epilepsy; GGE: Genetic Generalized Epilepsy; DEE: developmental epileptic encephalopathy.

III.6. **Discussion**

Our results indicate that 79.7% of children with new-onset seizures will achieve a 2YR after treatment initiation. The independent negative predictors of a 2YR include the presence and severity of IDD, the presence of an epileptogenic lesion on brain MRI and the number of pretreatment seizures. These results suggest that it is possible to identify children who are at risk of not achieving a 2YR based on variables obtained at the time of initial evaluation.

The percentage of children who achieved a 2YR in our study is comparable to the 74% rate reported in a previous study of 594 children with newly diagnosed epilepsy (21). The slightly lower remission rate in the previous study is likely due to a shorter follow-up period (median of 5.3 years compared to 7.4 years in our study) and a younger age at seizure onset (median of 5.3 years compared to 6.7 years in our study). Both studies, however, are consistent in showing that most children with new-onset seizures will reach a 2YR at some point during their clinical course, with most remissions occurring in the early years following treatment initiation.

Our data ascertaining that the presence and severity of IDD is one of the key factors impacting the likelihood of achieving a 2YR is consistent with the findings of previous studies (22–24). This is however the first study to clearly indicate that the presence and severity of IDD are the most significant baseline variables that influence the probability of attaining a 2YR. This conclusion was supported by the adjusted hazard ratio and the principal predictor variable of the recursive analysis, which showed that children with normal development had the highest likelihood of achieving a 2YR, those with mild to moderate IDD had a lower probability, and those with severe IDD had the lowest odds.

In this study, 27.8% of children were found to have an epileptogenic lesion on their brain MRI. Previous studies reported etiologically related neuroimaging abnormalities in 13%–18% of children with new-onset seizures (25–27). The higher percentage in our study is likely due to obtaining a dedicated epilepsy protocol MRI on all children, whereas prior studies evaluated children with brain CT and non-epilepsy protocol MRI (25,26,28) or excluded children with IDD (27). Those results emphasize the importance of obtaining an epilepsy protocol brain MRI as the presence of an epileptogenic lesion was a significant negative predictor for achieving a 2YR. Most studies evaluating the prognosis of childhood epilepsy have reported that a remote symptomatic etiology was predictive of poor seizure outcome (7,8,21,29,30). However, in our study, the recursive partitioning analysis found that this variable was only significant in children without evidence of IDD, indicating that the presence of IDD supersedes the detection of an epileptogenic lesion as a determinant of achieving a 2 YR. Although the relationship between the nature of

the pathologic substrate and medical refractoriness has been studied in adults (31–33), such analysis was beyond the scope of this study and will be the subject of future research.

Our findings are also consistent with other studies (8,9,34–37) that have shown that a higher number of pretreatment seizures is associated with a significantly lower probability of attaining a 2YR. However, the recursive partitioning analysis in our study found that this factor was only significant in children without IDD and without a lesion on brain MRI. Actually, nearly all children in this study with more than 100 seizures prior to treatment initiation experienced absence seizures, myoclonic seizures or epileptic spasms. Additionally, a subgroup analysis in our study revealed that the association between the number of pretreatment seizures and the likelihood of achieving a 2YR was only significant for children with focal-onset seizures. This finding is concordant with other observational studies (38,39), that when critically reviewed (40), documented that the relationship between high initial seizure frequency and poor outcome was only true for children experiencing focal impaired awareness seizures. Our data therefore support the conclusion that the type of epilepsy rather than the number of pretreatment seizures is the major variable that impacts outcome (40).

In our univariable analysis, we found that seizure onset within the first two years of life was associated with a significantly lower probability of achieving a 2YR, a result in line with previous studies (8,41,42). Nevertheless, in a multivariable analysis, we and others (9) found that there was no independent association between these variables. The divergent outcomes across different age groups are therefore more likely attributable to the prevalence of specific epilepsy syndromes in various age ranges. For instance, in our study, DEE was the most common diagnosis in children with seizure onset in the first two years of life, whereas GGE was the most prevalent among those with onset between 12 and 18 years.

Previous studies that evaluated the prognostic value of IED have yielded conflicting results. While some investigators found no significant association between prognosis and the presence of IED (8,21,24), others indicated that their presence was associated with a poorer outcome (41). Those studies however only assessed for the presence or absence of any type of IED (8,21,24) or at best categorized them into focal or generalized discharges (41). In our study, we divided the IED into four types and found that symptomatic generalized discharges and focal non-maturational discharges were associated with a significantly lower likelihood of attaining a 2YR in the univariable analysis. This association was however not significant in the multivariable analysis with the recursive partitioning analysis indicating that the coexistence of IDD in the case of symptomatic generalized discharges and epileptogenic lesions in the case of focal non-

maturational discharges overshadowed the importance of those types of IEDs as significant negative predictor variables.

Our study has several strengths that make its findings robust and reliable. Those include its prospective design and the inclusion of a large number of consecutive children referred from all governorates of the country, which enhances the generalizability of the results. Additionally, the study evaluated many variables that might impact prognosis and included a long-term follow-up, which allowed for a comprehensive evaluation of the outcomes. Furthermore, the seizures and epilepsies were classified according to the ILAE guidelines, providing a standardized and reliable classification system. Finally, this study not only confirmed the negative association between certain variables and the probability of a 2YR but is the first to perform a recursive analysis that allowed for a prioritization and splitting of those independent factors. Our study has also several limitations that need to be acknowledged. Firstly, the duration of follow-up was variable, which might have influenced the results. Secondly, some children were evaluated with a 1.5 Tesla MRI, which might have led to an underestimation of epileptogenic lesions. Furthermore, the serum levels of the newer ASMs were not routinely checked, and we relied on the information provided by caregivers or the parents regarding treatment adherence for these particular ASMs. In addition, in children younger than 6 years of age, we relied on the Denver Development Screening Test to assess for the presence and severity of IDD without confirmation from another assessment tool. Finally, genetic testing was not systematically obtained, especially in children with a DEE, which might have impacted the results. Future studies should aim to validate and expand upon the predictive variables identified in our investigation and to assess their generalizability to diverse populations.

III.7. **Conclusion**

This study provides valuable insights into the prognosis of children with new-onset seizures. The results indicate that the likelihood of achieving a 2YR can be assessed at the time of the initial evaluation, providing additional perspectives for counseling patients and their parents. The findings will allow for a timely selection of children who might require close follow-up or early neurosurgical intervention, or for management with investigational treatments.

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Chapter IV. Drug resistant epilepsy: Predictive factors in different childhood epilepsy syndrome groups

IV.1. **Background**

Until recently, there was no clear definition of drug resistant epilepsy, and epidemiological studies studying remission were for all intents also studying pharmacoresistance, assuming that not being in remission was equivalent to pharmacoresistance. The number of ASMs that needs to be failed for a patient to be marked as drug resistant was also largely debated. The ILAE however adopted the failure of two appropriately chosen ASM schedules in defining drug resistant epilepsy. This definition is of great importance in clinical practice as it allows early selection of candidates for epilepsy surgery and referral to a comprehensive epilepsy center, which may improve prognosis and reduce comorbidities.

This part of the study aims to look at the predictors of drug resistant epilepsy using the latest ILAE definition, regardless of whether a two-year seizure freedom period had been achieved. Since epilepsy is a dynamic process, patients may experience a two-year seizure free period then develop drug resistance. Conversely, patients who are marked as drug resistant may achieve seizure freedom later on. We also wanted to conduct the analysis separately for each epilepsy syndrome group, since we hypothesized that the clinical predictors of drug resistance would vary across different syndromes, given the variability in clinical characteristics among them.

IV.2. **Abstract**

Purpose: Drug resistant epilepsy (DRE) is a major challenge leading to a broad range of physical, cognitive and behavioral comorbidities and a higher rate of mortality. This study aims to evaluate predictors of DRE among different childhood epilepsy syndrome groups.

Methods: A prospective cohort of 676 patients with new onset seizures, initiated on treatment with antiseizure medication was evaluated. DRE was defined as failure to achieve seizure control on adequate trials of two well-tolerated and appropriately chosen antiseizure medication (ASM) regimens. Logistic regression analysis was performed to identify predictors of DRE within each epilepsy group.

Results: 29.3 % of children were resistant to treatment with ASMs. The highest percentage of DRE was found for the developmental and epileptic encephalopathies (77.7%), followed by the focal non-maturational epilepsies (31.5%). Within the genetic generalized epilepsies, factors associated with DRE were younger age at seizure onset and experiencing multiple seizure types. Within the focal non-maturational epilepsy, younger age at epilepsy onset, detection of an epileptogenic lesion on brain MRI, experiencing multiple seizure types, and having a greater number of pretreatment seizures were significant predictors of drug resistance. Within the developmental and epileptic encephalopathies, experiencing tonic or focal impaired awarness seizures predicted drug resistance.

Conclusion: Our results indicate DRE can be predicted by monitoring different clinical variables in different epilepsy groups. These findings may guide clinicians in identifying children at risk of DRE to intervene early on.

Keywords: Children and adolescents, Drug resistant epilepsy, genetic generalized epilepsies, focal non-maturational epilepsy, developmental and epileptic encephalopathies.

IV.3. **Introduction**

Epilepsy is recognized as one of the most prevalent neurological condition in childhood (1). Although many children with epilepsy respond favorably to antiseizure medications (ASMs), some continue to have seizures and develop drug resistant epilepsy (DRE). According to the International League Against Epilepsy (ILAE), DRE is defined as the inability to achieve sustained seizure freedom despite adequate trials of two well-tolerated and appropriately chosen ASM regimens, whether administered as monotherapy or in combination (2). Children with DRE experience a broad range of physical, cognitive and behavioral comorbidities and have a higher mortality rate (3–6).

Previous studies have reported varying estimates regarding the prevalence of DRE in children, with reported rates ranging from 7% to 49% (7). Some of this variability can be attributed to differences in the study populations and the specific definition of DRE used. Studies investigating predictors of drug resistance have also identified diverse risk factors with the most frequently reported consisting of: a younger age at onset of epilepsy (8,9), experiencing multiple seizure types (10–12), higher initial seizure frequency (13–15), greater number of pretreatment seizures (16), neurological deficits (8–11,16), and identification of a symptomatic etiology (13,15,16).

A major limitation of previous studies is that the assessment of factors predicting drug resistance was evaluated without considering the specific epilepsy syndrome. It was correctly argued that studies that lump together all epilepsy types are skewed towards the more prevalent types within the population (17). Additionally, due to the variability in clinical characteristics among different epilepsy syndromes, prognostic variables may differ across various groups. Therefore, conducting separate analyses on well-defined syndromes can provide more valuable insight into the predictors of drug resistance within each category. Another issue in previous studies is the retrospective nature of some, which may introduce a recruitment and information biases. To mitigate these limitations, it is advantageous to identify patients with new-onset epilepsy and follow them prospectively. (17).

This study aims to evaluate predictors of DRE among different childhood epilepsy syndrome groups in a cohort of children with new-onset seizures, using the most recent ILAE definition of drug resistance and classification of epilepsies (18,19).

IV.4. **Materials and methods**

IV.4.1. Study Design

Data are from an ongoing prospective study on children with new onset seizures conducted at the American University of Beirut Medical Center (AUBMC). This is a centralized study conducted in association with the Lebanese Chapter of the International League against Epilepsy (ILAE) whereby pediatric neurologists from all governorates of Lebanon have been referring children with new onset seizures to the AUBMC where a full clinical evaluation and extensive workup are performed.

The work-up included a detailed history and a thorough description of the spells obtained from the patient and an eyewitness, complete physical and neurological examinations, a 3-hour sleep deprived video-EEG recording interpreted by two experienced epileptologists, and an epilepsy protocol brain MRI interpreted by a neuroradiologist. Both epileptologists and the neuroradiologist were blinded to the patient's clinical history. Patients with acute symptomatic seizures, those with a history of alcohol or drug abuse, patients previously diagnosed with functional seizures, children with febrile seizures, and pregnant women were excluded. Patients were subsequently evaluated by telephone consultations and follow-up visits with repeat EEGs as clinically indicated. At each follow-up visit or phone call, information about seizure frequency, changes in antiseizure medication (ASM) therapy or posology, adverse events and adherence to treatment were systematically recorded. Adherence to treatment was monitored through inquiries made to the caregiver/patient regarding the administration of ASM as prescribed. For children receiving valproate, carbamazepine, phenytoin or phenobarbital, routine monitoring of serum levels for these medications was conducted. However, due to the unavailability of local facilities for checking serum levels of newer ASMs and the high associated costs involved, which were not affordable for most patients or their parents, the serum levels of these drugs were rarely monitored. Children presenting with psychiatric symptoms on follow-up visits were referred to a pediatric psychiatrist for evaluation.

IV.4.2. Inclusion/exclusion criteria

For the purpose of this study, we included children below 18 years of age who experienced one or more unprovoked seizures between March 2010 and May 2016 and were initiated on ASM treatment. Children who did not undergo an adequate trial of at least two ASMs were excluded as were those with a follow-up less than two years.

IV.4.3. Definition of outcome

Children were considered to have DRE if they failed treatment with two tolerated and appropriately chosen ASMs for the epilepsy syndromes Instances where ASM failure occurred due to drug adverse events on non-adherence were not considered failures in the criteria for DRE according to the ILAE criteria.

IV.4.4. Classification of seizure types and epilepsy groups

Seizure types were classified according to the latest ILAE 2017 classification of seizure types (20). The case report file of each child was entirely reviewed at last follow-up to ensure that the correct electroclinical syndrome was made. The electroclinical syndromes were classified according to the latest ILAE classification of the epilepsies (19) and the recent ILAE classification and definition of epilepsy syndromes (18). Four main epilepsy groups were identified: (1) self-limited focal epilepsies (SeLFEs), (2) genetic generalized epilepsies (GGEs)- comprising both idiopathic and genetic generalized epilepsies, (3) focal non-maturational epilepsy, and (4) developmental and epileptic encephalopathies (DEEs).

IV.4.5. Ethical approval

This study was approved by the Institutional Review Board of the AUBMC, and all children enrolled in this study had an informed consent signed by one of their parents.

IV.4.6. Brain MRI and classification of neuro-imaging findings

Brain MRIs were obtained from a 1.5 or 3T scanner (Ingenia; Phillips Healthcare) using an imaging-acquisition protocol that included 3D T1 (1 mm slice thickness) and 3D fast fluid-attenuated inversion recovery (FLAIR; 0.9- or 1-mm slice thickness) of the whole brain with multiplanar reconstruction, axial and coronal inversion recovery (2 mm slice thickness), axial T2 TSE and T2 FFE (4 mm slide thickness) and axial diffusion weighted images (4-5 mm slice thickness). The 3D images were obtained with no interslice gap.

MRI findings were classified as epileptogenic or non-epileptogenic based on previously published criteria (14,16). MRI abnormalities consisting of isolated subcortical lesions or abnormal signal, nonspecific white matter hyperintensities, hydrocephalus, and brain atrophy were considered incidental findings.

IV.4.7. Sleep deprived Electroencephalogram (EEG) and classification of EEG findings

The EEGs were recorded on digital Nicolet machines (Natus^{R} Neurodiagnostics) with electrodes placed according to the International 10-20 system. At the initial visit, a 3-hour sleep deprived video-EEG with sleep recording was recorded from all patients. At each follow-up visit, a 60-minute sleep deprived EEG recording was performed. The EEG obtained at the initial visit were stratified according to the presence or absence of interictal epileptiform discharges (IEDs). Focal IEDs were classified based on their topography, morphology and presence or absence of focal slowing into focal maturational or focal non-maturational discharges (22). The generalized spike wave discharges (GSWD) of the type seen in patients with a genetic generalized epilepsy (frequency of more than 2.5 Hz associated with a normal background) were labeled as idiopathic generalized discharges (22). The GSWD of the type seen in patients with a developmental and epileptic encephalopathy (frequency of less than 2.5 Hz associated with a slow and disorganized background with or without concomitant focal or multifocal IEDs) were labelled as symptomatic generalized discharges.

IV.4.8. Assessment of Intellectual and Developmental Delay

All patients underwent an assessment to evaluate for the presence and severity of intellectual and developmental delay (IDD). Children younger than 6 years of age were evaluated using the Denver Development Screening Test (18). Older children were assessed according to the Diagnostic and Statistical Manual of Mental Disorders criteria, which classifies intellectual delay as mild, moderate, severe, or profound based on deficits in intellectual functioning as well as difficulties in conceptual, social, and practical areas of living (19). For example, children with mild intellectual delay may struggle with learning abilities and exhibit immaturity in social interactions, with communication and language skills that are more concrete than expected for their age. Children with moderate intellectual delay display marked limitations compared to their peers, with significant differences in social and communicative behavior. However, children with mild and moderate intellectual delay can still care for their personal needs, including eating, dressing and hygiene. Children with severe and profound intellectual delay have limited or very limited language development and have substantial limitations in the conceptual domains. They require support or are completely dependent on others for all activities of daily living (19). For the purpose of our analysis, we combined children with severe and profound delays into a single category, and included three groups of IDD (mild, moderate, or severe). To ensure the accuracy and consistency of the assessments, research fellows with specialized training in administering these tests were responsible for conducting the evaluation and scoring the degree of deficit. These chosen assessment tools were

selected based on factors such as feasibility in terms of cost, accessibility, time requirements, and training considerations.

IV.4.9. Treatment

The decision to initiate ASMs and the type of medication prescribed was made by the treating physician. Typically, children were initially started on monotherapy with the dose titrated upward till the target dose was reached. In case of seizure recurrence, the dose was gradually increased to the highest tolerated dose before introducing a second ASM as alternative monotherapy or as part of a dual therapy. If the child was experiencing significant adverse events, the ASM was switched to another drug.

IV.4.10. Variables

The following data was collected for each child : (1) demographics: (gender, age at enrollment, place of origin, residence, number of household members, income, and third-party payers); (2) disease characteristics (age at seizure onset, seizure types throughout follow-up, number of seizure types throughout follow-up ; (3) epilepsy risk factors (family history of epilepsy, parental consanguinity, perinatal insult, febrile seizures, head trauma, CNS infection); (4) IDD (presence and severity); (5) IED types on initial or subsequent EEG; (6) Brain MRI results (presence or absence of epileptogenic lesion). Clinical course characteristics included: (1) epilepsy drug responsiveness (Drug responsive epilepsy, drug resistance epilepsy); (2) type of first ASM failed; (3) type of second ASM failed.

IV.4.11. Statistical Analysis

Descriptive results were reported for the demographic and clinical characteristics. Univariable logistic regression analysis was done to explore the unadjusted association between different variables and DRE within each epilepsy group. Variables yielding p-values <0.05 were then included in the multivariable logistic regression analysis to assess independent factors predictive of DRE. Significance level was set at 5%. All analysis was done using SPSS.

IV.5. **Results**

827 children with new-onset seizures and initiated on ASM treatment were enrolled. Out of those, 150 children were excluded for the following reasons: 90 had a follow-up of less than 2 years on ASM treatment and 61 did not have an adequate trial of two ASMs. As a result, a total of 676 children were included in the final analysis with 198 (29.3%) diagnosed with drug resistant epilepsy.

IV.5.1. Characteristics of the study sample

Demographic and clinical characteristics are presented in Table 1. Most of the children were boys (59.9%) and the median age at seizure onset was 6.4 years (interquartile range (IQR) 2.1-10.9). The follow-up ranged from 2 to 12.4 years, with a median of 7.7 years (IQR 6.0-9.3). The most common seizure types encountered throughout the duration of follow-up were focal impaired awareness seizures (FIAS) in 293 children (43.3%), followed by focal to bilateral tonic-clonic seizures (FBTC) in 217 children (32.1%). The majority of children experienced a single seizure type throughout follow-up (63.0%), while 49 (7.2%) experienced three types or more. The number of seizures prior to treatment initiation ranged from 1 to5 in 351 children (51.9%), while 228 children (33.7%) experienced more than 100 seizures. The vast majority of children with more than 100 seizures t prior to treatment initiation were experiencing myoclonic jerks, absences, or epileptic spasms.

Psychiatric disorders were diagnosed in 75 children (13.7%), while varying degrees of IDD were observed in 186 (27.5%) children. A family history of epilepsy was present in 201 children (29.7%) and 160 (23.7%) were born from consanguineous marriage. IEDs on EEG were detected in 525 children (77.7%), and an epileptogenic lesion was found on the brain MRI of 195 children (29.2%). The most commonly prescribed ASM throughout the follow-up period was valproate in 494 children (73.1%), followed by levetiracetam in 212 children (31.4%), and carbamazepine in 141 children (20.9%).

Table 1 Demographic and clinical characteristics of the study sample (N=676) and follow-up period.

Variable	Mean ±STD	Range	Median (IQR)
Age at seizure onset (years)	6.9±5.0	0.5-17.6	6.4 (2.1-10.9)
Duration of follow-up (years)	7.4±2.4	2-12.4	7.7 (6.0-9.3)
Variable		**N (%)**	
Gender			
Male		405 (59.9)	
Female		271 (40.1)	
Seizure types throughout follow-up			
Focal impaired awareness seizures		293 (43.3)	
Focal to bilateral tonic-clonic seizures		217 (32.1)	
Focal aware seizures		113 (16.7)	
Generalized onset tonic-clonic seizures		92 (13.6)	
Typical absence seizures		76 (11.2)	
Myoclonic jerks		59 (8.7)	
Epileptic spasms		71 (10.5)	
Tonic seizures		25 (3.7)	
Atypical absence seizures		10 (1.5)	
Others*		26 (3.8)	
Number of seizure types throughout follow-up			
1 type		426 (63.0)	
2 types		201 (29.7)	
3 types or more		49 (7.2)	
Pretreatment number of seizures			
1-5		351 (51.9)	
6-10		35 (5.2)	
11-100		62 (9.2)	
≥100		228 (33.7)	
Psychiatric disorders (N=548)[a]			
Yes		75 (13.7)	
No		473 (86.3)	
Intellectual and developmental delay			
None		490 (72.5)	
mild		58 (8.6)	
moderate		53 (7.8)	
severe		75 (11.1)	
Presence of epilepsy risk factors			
Yes		450 (66.6)	
Family history		201 (29.7)	
Consanguinity		160 (23.7)	
Perinatal insult		112 (16.6)	
Febrile seizures		87 (12.9)	
Head trauma		36 (5.3)	
CNS infection		15 (2.2)	
IEDs on EEG throughout follow-up			
No		151 (22.3)	
Yes		525 (77.7)	
IED type on EEG			
Focal			
Maturational		96 (14.2)	
Non-maturational		182 (26.9)	

Generalized	
Idiopathic	144 (21.3)
Symptomatic	103 (15.2)
Epileptogenic Lesion on MRI (N= 668)[b]	
Yes	195 (29.2)
No	473 (70.8)
Epilepsy classification	
Self-limited focal epilepsy	110 (16.3)
Genetic generalized epilepsy	146 (21.6)
Focal non-maturational epilepsy	317 (46.9)
Developmental and epileptic encephalopathies	103 (15.2)
ASMs received throughout follow-up	
Valproate	494 (73.1)
Levetiracetam	212 (31.4)
Carbamazepine	141 (20.9)
Oxcarbazepine	95 (14.1)
Clonazepam	102 (15.1)
Topiramate	67 (9.9)
Vigabatrin	71 (10.5)
Lamotrigine	61 (9.0)
Lacosamide	26 (3.8)
Ethosuximide	25 (3.7)
Phenobarbital	25 (3.7)
Other****	99 (14.6%)
Drug responsiveness	
Drug responsive epilepsy	478 (70.7)
Drug resistant epilepsy	198 (29.3)

**Other ASMs include ACTH [24 children (3.6%)], phenytoin [14 (2.1%)], steroids [13 (1.9%)], clobazam [13 (1.9%)], perampanel [12 (1.8%)], acetazolamide [7 (1.0%)], zonisamide [4 (0.6%)], potassium bromide [5 (0.7%)], sulthiame [4 (0.6%)], pregabalin [2 (0.3%), and gabapentin [1 (0.1%)].
STD: Standard deviation, IQR: Interquartile range, IEDs: Interictal epileptiform discharges, EEG: Electroencephalogram, MRI: Magnetic resonance imaging, ASMs: Anti-seizure medications.
*Other seizure types include: Unknown-onset tonic-clonic seizures in 7 children (1.0%), atonic seizures in 11 children (1.6%), myoclonic absence and myoclonic atonic seizures in 3 children each (0.4%)
[a] Psychiatric comorbidity could not be assessed in 128 children due to severe delay or age at last follow-up less than 5 years.
[b] a brain MRI was not obtained in 8 children.

IV.5.2. Epilepsy group classification and response to ASM

Upon reviewing the case report file of each child at the last follow for accurate diagnosis and syndrome classification, 317 (46.9%) were diagnosed with a focal non-maturational epilepsy, 146 (21.6%) with a GGE, 110 (16.3%) with a SeLFE, and 103 (15.2%) with a DEE.

The prevalence of drug resistance across different epilepsy groups is presented in figure 1. The highest rate of drug resistance was in children diagnosed with a DEE (77.7%). The frequency of drug resistance was high for all electroclinical syndromes within this group, with a slightly better outcome observed in infantile epileptic spasms syndrome (IESS) and epilepsy with myoclonic-atonic seizures (EMAtS) (68.9% and 50% of cases having drug resistance respectively).

Children diagnosed with a focal non-maturational epilepsy had the second highest rate of drug resistance (31.5%).

Children diagnosed with a GGEs had a substantially better outcome with only 9.6% diagnosed with a DRE. The highest rate of drug resistance within this group was observed in children with myoclonic epilepsy in infancy (MEI) and childhood absence epilepsy (CAE) (50% and 17.1% of cases having drug resistance respectively).

The best outcome was seen in children diagnosed with SeLFEs with only 4 children (3.6%) developing DRE. These children were diagnosed with self-limited focal epilepsy with centrotemporal spikes (SLECTS) and subsequently entered into remission on prolonged follow-up, following the natural course of the disease.

The median time to drug resistance also varied between different epilepsy groups: 0.73 years (IQR: 0.39-1.76) in GGEs, 1.68 years (IQR: 0.54-3.11) for SeLFEs, 1.29 years (IQR: 0.63-2.88) for the focal non-maturational epilepsy, and 0.71 years (IQR 0.27-2.30) for the DEEs.

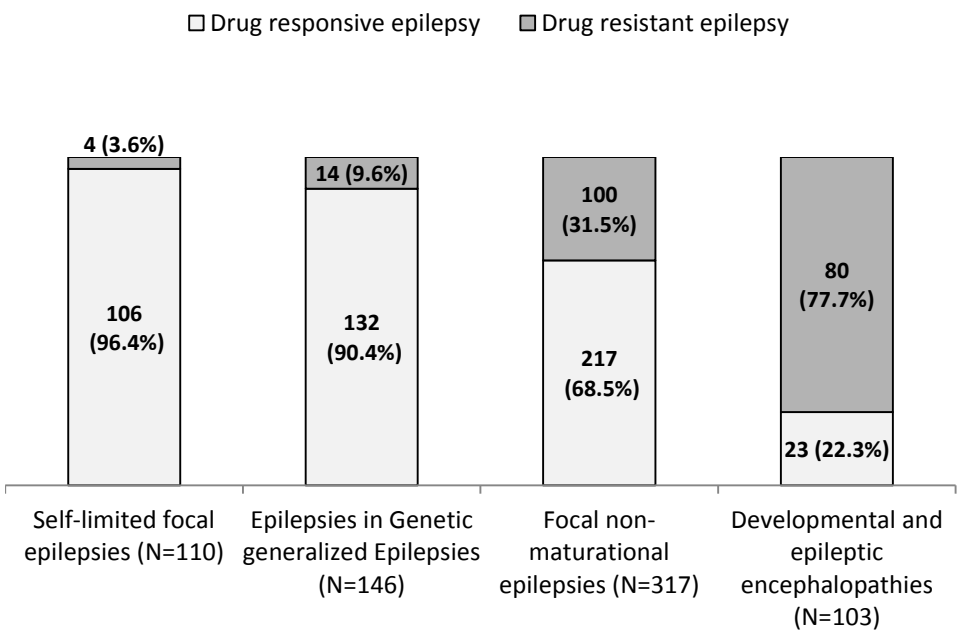

Figure 1 Drug responsiveness stratified according to the classification of epilepsies.

The first two appropriately chosen ASMs that failed due to lack of efficacy in children who developed DRE, stratified according to the classification of epilepsies are presented in table 2. Of the 100 children with DRE and having a focal non-maturational epilepsy, 33 (33%) received non-pharmacologic treatment. This comprised 12 (12%) put on a vagus nerve stimulator and 21(21%) undergoing surgery. Similarly, of the 80 children with DRE and having a DEE, 19 (23.8%) received non-pharmacologic treatment. This included 3 (3.8%) children put on a ketogenic diet, 17 (21.3%) put on vagus nerve stimulation, and 2 (2.5%) undergoing surgery.

At last follow-up, 67 (33.8%) of the children diagnosed with DRE were in terminal one-year remission.

Table 2 First two adequate ASMs failed due to lack of efficacy in drug resistant patients, stratified according to the classification of epilepsies.

	Self-limited focal epilepsies N= 4		Genetic generalized Epilepsies N=14		Focal non-maturational epilepsy N=100		Developmental and epileptic encephalopathies N=80	
Treatment regimen	Failed as 1st ASM	Failed as 2nd ASM	Failed as 1st ASM	Failed as 2nd ASM	Failed as 1st ASM	Failed as 2nd ASM	Failed as 1st ASM	Failed as 2nd ASM
Valproate	3	1	13	1	62	10	41	9
Levetiracetam		2	1	4	3	36	3	17
Clonazepam	1	1		1	2	7		11
Topiramate				2	3	3	4	10
Lamotrigine				1	2	4		7
Phenobarbital					2	2	5	2
Oxcarbazepine					5	16	1	1
Carbamazepine					18	17		
Ethosuximide				5				
Phenytoin					3			
Lacosamide						3		
Vigabatrin					1	1	26	11
ACTH								4
Hydrocortisone								8

IV.5.3. Predictors of drug resistance according to the classification of epilepsies

IV.5.3.1. Self-limited focal epilepsies

Predictors of drug resistance within SeLFE could not be identified due to the very small number of cases diagnosed with a DRE (only 4 children diagnosed with SLECTS failed two ASMs).

IV.5.3.2. Genetic Generalized epilepsies

Univariable analysis revealed that older age at epilepsy onset was predictive of a lower probability of developing drug resistance [p= 0.001; odd ratio (OR) 0.8 (95% confidence interval 0.70-0.91]. Factors predictive of a higher probability of drug resistance were having myoclonic jerks [p=0.004 OR 5.40 (1.69-17.26)], experiencing 3 or more seizure types [p=0.015, OR 12.13 (1.63-89.91)], and comorbidity with a diagnosis of psychiatric disorders [p=0.027 OR 4.44 (1.20-16.62)].

On multivariable analysis, older age at epilepsy onset [p= 0.001, OR 0.75 (0.63-0.88)] remained significantly predictive of a lower odds of DRE. Experiencing multiple seizure types was the most important predictor of drug resistance. This was particular for patients having 3 seizure types (GOTC, absence, and myoclonic jerks), [p=0.001, OR 56.39 (5.27-602.86)]. Patients experiencing two types of seizures were also at increased risk of drug resistance [p=0.037, OR 4.35 (1.09-17.35)].

IV.5.3.3. Focal non-maturational epilepsy

In univariable analysis, significant predictors of drug resistance were: younger age at epilepsy onset [p=0.001 OR 0.92 (0.87-0.96)], experiencing FAS [p<0.001 OR 3.32 (1.93-5.71)], experiencing FIAS (p=0.021 OR 1.91 (1.10-3.31), having multiple seizure types [2 types: p=0.002, OR 2.29 (1.36-3.87); 3 types or more: p=0.001, OR 5.46 (2.04-14.63)], having a greater number of pretreatment seizures (11-100 seizures vs.1: p=0.002, OR 2.94 (1.48-5.81); ≥100 seizures vs. 1: p <0.001, OR 6.47 (3.02-13.84)], presence of interictal epileptiform discharges on EEG (p<0.001, OR 2.82 (1.67-4.74)], detection of an epileptogenic lesion on brain MRI [p<0.001, OR 4.47 (2.69-7.41)], and the presence and severity of ID/DD [mild delay: p=0.014, OR 2.55 (1.21-5.40); moderate delay: p=0.006, OR 3.07 (1.38-6.2); severe delay: p=0.001, OR 4.29 (1.81-10.21)].

In multivariable analysis, only younger age at epilepsy onset (p=0.048, OR 0.94 (0.88-0.99)); detection of an epileptogenic lesion on brain MRI (p<0.001, OR 3.73 (2.11-6.58); experiencing multiple seizure types (2 types: p=0.002, OR 2.57 (1.43-4.64); ≥ 3 types: p=0.008, OR 4.81 (1.51-15.34)); and having a greater number of pretreatment seizures (11-100 seizures: p= 0.022, OR 2.45 (1.14-5.29); ≥100 seizures: p<0.001, OR 4.80 (2.10-10.97)) remained significant predictors of DRE.

IV.5.3.4. Developmental and/or epileptic encephalopathies

Within DEEs, univariable analysis found that experiencing tonic seizures or FIAS was significantly predictive of a higher probability of DRE (p=0.033, OR 9.42 (1.2-74.0) for both).

Conversely, experiencing spasms was associated with a lower odds of drug resistance (p=0.036OR 0.25 (0.07-0.91)). Experiencing multiple seizure types was also predictive of DRE [2 types: p=0.095, OR 2.35 (0.86-6.44); 3 types or more: p=0.031, OR 10.23 (1.24-84.66)].

On multivariable analysis, experiencing multiple seizure types was no longer predictive of drug resistance, but it was rather experiencing specific seizure types: experiencing tonic seizures (p=0.039, OR 8.92 (1.12-71.34)) or FIAS (p=0.039, OR 8.92 (1.12-71.34) were predictive of a higher odds of drug resistance.

Univariable and multivariable results for all 3 epilepsy groups are presented in Tables 3 and 4 respectively.

Table 3 Univariable associations for drug resistance and different variables according to the classification of epilepsies.

	Genetic generalized epilepsies		Focal non-maturational epilepsies		Developmental and epileptic encephalopathies	
Variable	**p-value**	**Unadjusted OR (95% CI)**	**p-value**	**Unadjusted OR (95% CI)**	**p-value**	**Unadjusted OR (95% CI)**
Gender	**0.705**	1.23 (0.41-3.73)	0.108	1.48 (0.92-2.41)	0.887	0.93 (0.36-2.42)
Age at onset of epilepsy	**0.001**	0.80 (0.70-0.91)	0.001	0.92 (0.87-0.96)	0.114	1.445 (0.92-2.29)
Seizure types throughout follow-up						
GOTC	0.127	0.41 (0.13-1.28)		-	0.060	0.29 (0.08-1.05)
Absence	**0.05**	3.78 (1.01-14.17)		-	0.949	0.95 (0.23-3.97)
Myoclonic Jerks	**0.004**	5.40 (1.69-17.26)		-	0.102	3.62 (0.77-16.93)
Spams		-		-	**0.036**	0.25 (0.07-0.91)
Tonic		-		-	**0.033**	9.42 (1.2-74.0)
Atonic		-		-	0.999	-
FAS		-	**<0.001**	3.32 (1.93-5.71)	0.999	-
FIAS		-	**0.021**	1.91 (1.10-3.31)	**0.033**	9.42 (1.20-74.0)
FBTC		-	0.387	0.81 (0.50-1.30)	0.999	-
Number of seizure types throughout follow-up						
1 type	Ref		Ref		Ref	
2 types	0.050	3.35 (1.00-11.22)	**0.002**	2.29 (1.36-3.87)	**0.095**	2.35 (0.86-6.44)
3 types or more	**0.015**	12.13 (1.63-89.91)	**0.001**	5.46 (2.04-14.63)	**0.031**	10.23 (1.24-84.66)
Pretreatment number of seizures						
1-5	Ref		Ref		Ref	
6-10	1	1	0.879	0.89 (0.32-2.54)	-	
11-100	1	1	**0.002**	2.94 (1.48-5.81)	1	1
≥100	0.997	1	**<0.001**	6.47 (3.02-13.84)	0.999	0
IEDs on EEG	0.110	0.10 (0.006-1.68)	**<0.001**	2.82 (1.67-4.74)	1	0

Epileptogenic lesion on MRI	0.328	3.21 (0.31-33.08)	**<0.001**	4.47 (2.69-7.41)	0.617	1.18 (0.51-2.78)
Psychiatric disorders	**0.027**	4.44 (1.20-16.62)	0.659	1.18 (0.55-2.54)	0.185	3.5 (0.55-22.30)
Intellectual and developmental delay						
No delay	Ref		Ref		Ref	
Mild IDD	0.149	3.57 (0.63-20.15)	**0.014**	2.55 (1.21-5.40)	0.108	0.22 (0.04-1.39)
Moderate IDD	1	0	**0.006**	3.07 (1.38-6.2)	0.211	0.33 (0.06-1.86)
Severe IDD	1	0	**0.001**	4.29 (1.81-10.21)	0.957	1.05 (0.19-5.71)
Presence of epilepsy Risk factors	0.348	1.79 (0.53-5.60)	0.379	0.80 (0.48-1.33)	0.218	1.81 (0.70-4.65)
Perinatal insult history	0.999	0	0.471	1.26 (0.67-2.37)	0.523	1.33 (0.55-3.25)
Head trauma History	0.774	1.37 (0.16-12.05)	0.550	0.73 (0.26-2.06)	0.821	1.30 (0.13-13.05)
CNS infection history	1	0	0.299	1.90 (0.57-6.38)	1	-
Consanguinity	0.172	2.26 (0.70-7.73)	0.246	1.38 (0.80-2.39)	0.280	1.65 (0.66-4.09)
Family history of epilepsy	0.126	2.38 (0.78-7.25)	0.128	0.66 (0.38-1.13)	0.369	1.60 (0.57-4.48)

OR: odds ratio. GOTC: generalized onset tonic-clonic seizures, FAS: focal aware seizures. FIAS: focal impaired-awareness seizures. FTBC: focal to bilateral tonic-clonic seizures, IEDs: Interictal Epileptiform Discharges, EEG: electroencephalogram, MRI: magnetic resonance imaging, IDD: intellectual and developmental delay, CNS: central nervous system.

Table 4 Multivariable logistic regression results for variables predictive of drug resistance according to the classification of epilepsies.

Variable	p-value	Adjusted OR (95% CI)
Genetic generalized epilepsies [a]		
Age at onset of epilepsy	**0.001**	0.75 (0.63-0.88)
Number of seizure types throughout follow-up		
1 type	Ref	-
2 types	**0.037**	4.35 (1.09-17.35)
3 types or more	**0.001**	56.39 (5.27-602.86)
Focal non-maturational epilepsies [b]		
Age at onset of epilepsy	**0.048**	0.94 (0.88-0.99)
Epileptogenic lesion on MRI	**<0.001**	3.73 (2.11-6.58)
Number of seizure types throughout follow-up		
1 type	Ref	
2 types	**0.002**	2.57 (1.43-4.64)
3 types or more	**0.008**	4.81 (1.51-15.34)
Pretreatment number of seizures		
1-5	Ref	
6-10	0.770	0.85 (0.78-2.59)
11-100	**0.022**	2.45 (1.14-5.29)
≥100	**<0.001**	4.80 (2.10-10.97)
Developmental epileptic encephalopathies [c]		
Tonic seizures	**0.039**	8.92 (1.12-71.34)
FIAS	**0.039**	8.92 (1.12-71.34)

OR: Odds ratio, CI: Confidence Interval, MRI: magnetic resonance imaging, FIAS: focal impaired awareness seizures.
[a] Method: Forward-Likelihood Ratio. Variables entered into the model: Age at onset of epilepsy, myoclonic Jerks, absence seizures, number of seizure types throughout follow-up, psychiatric disorders. Omnibus test of model coefficients p-value<0.001. Nagelkerke R Square=0.309, Hosmer and Lemeshow test p-value=0.923, Overall percentage=91%.
[b] Method: Forward- Likelihood Ratio. Variables entered into the model: Age at onset of epilepsy, FAS, FIAS, pretreatment number of seizures, number of seizure types throughout follow-up, epileptogenic lesion on MRI, IEDs on EEG throughout follow-up, developmental delay degree. Omnibus test of model coefficients p-value <0.001. Nagelkerke R Square=0.308, Hosmer and Lemeshow test p-value=0.150, Overall percentage=75.6%.
[c] Method: Forward- Likelihood Ratio. Variables entered into the model: Age at onset of epilepsy, tonic seizures, spasms, FIAS, number of seizure types throughout follow-up. Omnibus test of model coefficients p-value<0.001. Nagelkerke R Square=0.214, Hosmer and Lemeshow test p-value=0.808, Overall percentage=77.7%.

IV.6. **Discussion**

This study attempted to evaluate predictors of drug resistance after classification of the epilepsies. In comparison to studies that study all epilepsies together, our rationale yields more accurate results on the associations between different factors and drug resistance. This is particular for variables where there is a different directionality for the association. For example, older age at epilepsy onset was associated with a lower likelihood of DRE in patients diagnosed with a GGE, while it was associated with a higher likelihood of resistance in patients with a DEE. This effect modification would not have been detected without a subgroup analysis.

Our results revealed that 29.3 % of children with seizures were resistant to treatment with ASMs. This percentage closely aligns with the 27% pooled prevalence of DRE reported in a systematic review assessing epilepsy patients (7). Identifying patients at risk of developing DRE is important due to the significant impact of on quality of life, health care utilization and associated costs. In addition, it would be beneficial to predict the likely clinical course of a child's epilepsy within a short period after diagnosis. This could allow more informed parental counseling, prompt consideration of more aggressive medical treatment, and earlier consideration of neurosurgical or non-pharmacological interventions. A recent systematic review of the literature revealed that the most frequently reported predictors of DRE were the presence of neurological deficits, a diagnosis of symptomatic epilepsy, and EEG abnormalities (23) However, most of these studies included patients without specifying their epilepsy syndromes or without establishing correlations between predictors and each specific syndrome..

Our findings revealed that the highest prevalence of drug resistance was found in children diagnosed with developmental and epileptic encephalopathies (DEEs), with 77.7% of patients within that group exhibiting resistance to pharmacological treatment. This finding is not surprising as this group comprises epileptic syndromes such as Lennox Gastaut syndrome which is known to have a poor prognosis with persistent seizures and a high likelihood of drug resistance (18,24–27). Among the 103 children with DEEs included in our study, only 23 (22.3%) exhibited a positive response to medication, including 19 children diagnosed with infantile epileptic spasms syndrome (IESS). This suggests that IESS may have a more favorable prognosis compared to other DEEs. Moreover, our subgroup analysis focusing on children with IESS demonstrated that having spasms as the sole seizure type was significantly associated with drug responsiveness. This finding is concordant with a previous study that reported that the absence of other seizure types alongside spasms predicts a favorable prognosis in terms of seizure control (28). In contrast, experiencing tonic seizures or FIAS was associated with a higher likelihood of drug resistance. Although tonic seizures have rarely been reported as a sole predictor of resistance (29) , their inclusion as a mandatory seizure type for the diagnosis of Lennox-Gastaut syndrome

likely explains their association with drug resistance when stratifying correlations within the DEE group. As for FIAS, focal seizures have been identified as predictors of drug resistance in some studies comparing focal to the generalized seizures (30).

Children with focal non-maturational epilepsies had the second highest rate of DRE accounting for 31.5%. The multivariable analysis identified four factors as predictors of a higher likelihood of drug resistance. These included a younger age at seizure onset, the presence of an epileptogenic lesion on MRI, a greater number of pretreatment seizures, and experiencing multiple seizure types. Previous studies evaluating the prognosis of childhood epilepsy have consistently reported that a remote symptomatic etiology predicts poor seizure outcomes and the development of intractable epilepsy (13,31–33). Consistent with our study, younger age at seizure onset has also been associated with drug resistance in focal epilepsies (29,34). Furthermore, our findings align with other studies (13,35–37) indicating that a higher number of pretreatment seizures significantly reduces the likelihood of achieving remission. The presence of multiple seizure types remains a consistent predictor of treatment resistance within this group of epilepsy, in agreement with previous research (10,31,38). This predictor is particularly important to consider in children with focal seizures but no detectable structural lesion on MRI.

Children with a GGE had a 9.6 % risk of becoming drug resistant, a percentage that is slightly lower than the 12.1% observed in adults (39). This can be partly explained by the fact that most of those syndromes will persist throughout adulthood and thus a longer follow-up period may increase the risk of becoming resistant to ASMs. The percentage of DRE was even higher (35 %) in a study that included only specific epilepsy syndrome of the GGE like JME (40). In our study, two variables predictive of drug resistance in children with GGE were identified; younger age at seizure onset and having multiple seizure types. Previous studies (40,41) also found that younger seizure onset in GGE was correlated to DRE, which may reflect more severe brain dysfunction probably related to genetic components (38). Moreover, our finding that having multiple seizure types is a predictor of drug resistance in children with GGE is in agreement with previous studies on JME (40), JAE (42), and CAE (42–44). Experiencing myoclonus as a seizure type was associated with drug resistance only in univariable analysis, likely because this variable is inter-related with having multiple seizure types. Previous studies on GGE, specifically on JME, have identified an association between drug resistance and having psychiatric comorbidity (40). Although the presence of psychiatric comorbidity was associated with DRE in GGEs in univariable analysis, it did not reach statistical significance in multivariable analysis in this study. It also possible that psychiatric comorbidity was underreported in this age group since children were not routinely seen by a neuropsychiatrist. Further large scale studies are warranted to distinguish whether this finding is true for all GGEs. In addition, although some electrographic findings have been found to help predict drug resistance in IGE patients, the impact of EEG in this setting is controversial and

different studies have come to remarkably different conclusions (45,46). In our study, this factor was not a significant predictor likely because a detailed analysis of different EEG patterns wasn't performed.

In this study, only four children with self-limited epilepsy with centro-temporal spikes (SLECTS), accounting to 3.6% of children with SeLFE, met the definition for drug resistance. Those children, however, were able to achieve remission on later follow-up. SeLFEs are known to have an excellent prognosis and a spontaneous seizure remission during adolescence, however drug resistance may occur during the epilepsy active phase (47). We were unable to identify predictors of drug resistance within SeLFEs due the small sample size and low number of patients experiencing resistance. Larger scale studies on children with SeLFEs, specifically SLECTS, are warranted to delineate factors associated with poor seizure control before the disease naturally resolves.

The strengths of this study is its prospective design, the inclusion of a large number of children referred from all governorates of the country, and the use of the latest ILAE definition of DRE and classification of epilepsy syndromes. Our study has however several limitations that need to be recognized. The duration of follow-up was variable with a minimum of two-years which may have led to an underestimation of DRE; Some patients who were initially drug responsive might have later on evolved into drug resistance. Furthermore, the presence of an epileptogenic lesion on brain MRI may have been undetected in some children who were evaluated with a 1.5 Tesla MRI. In addition, in children younger than 6 years of age, we relied on the Denver Development Screening Test to assess for the presence and severity of IDD without confirmation from another assessment tool. Concerning assessment of adherence to ASMs, the serum levels of the newer ASMs were not routinely checked, and we relied on the information provided by caregivers or the parents regarding treatment adherence for these particular ASMs. Finally, genetic testing which is an important factor in epilepsy outcome was not systematically obtained, especially in children with a DEE, which might have impacted the results.

IV.7. **Conclusion**

Our study suggests that different epilepsy syndromes have different predictors of drug resistance. The risk of developing intractable epilepsy can be predicted within different syndromes based on clinical variables available during the disease course. Those findings will enable selecting children requiring close monitoring or non-medical interventions in a timely manner.

IV.8. **References**

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Chapter V. Psychopathology and associated factors in children and adolescents with epilepsy

V.1. Background

A comprehensive and multidisciplinary approach in the management of epilepsy should not only focus on seizure control, but also target epilepsy comorbidities, which are especially frequent in drug resistant epilepsy. Epidemiological studies have found that children with poor seizure control have a higher rate of psychiatric comorbidity, such as anxiety disorders, depression, attention-deficit/hyperactivity disorder (ADHD), and autism spectrum disorders. The bidirectional relationship between epilepsy and these psychiatric conditions further complicates the clinical picture, as seizures can trigger or exacerbate psychiatric symptoms, and conversely, psychiatric issues can impact seizure control and overall quality of life.

Children living in developing countries may face unique challenges as psychiatric comorbidities may be underdiagnosed and undertreated. Data on psychiatric comorbidities in children with epilepsy residing in Lebanon is lacking. In this part of the study we wanted to evaluate the frequency of psychiatric comorbidity in children with epilepsy residing in Lebanon, and to study its association with different clinical variables such as seizure control.

V.2. **Abstract**

Purpose: Children with epilepsy have an increased risk of developing psychiatric comorbidity. This study aims to evaluate the prevalence of psychiatric disorders and associated factors in a large cohort of children with epilepsy.

Methods: A medical record analysis was done for a cohort of 568 epileptic children recruited at the time of seizure onset at the American University of Beirut Medical Center (AUBMC). Psychiatric disorders were classified into internalizing or externalizing disorders based on DSM-5 criteria, and were considered present if the child was referred and diagnosed by a pediatric psychiatrist, therapist, or neurologist, or if the medical record provided clear evidence of taking a medication for a psychiatric disorder. Multiple logistic regression was used to identify factors associated to psychiatric disorders.

Results: 75 children (13.2%) of children with epilepsy were diagnosed with a psychiatric disorder, among which 30 (5.3%) had and internalizing disorder and 47 (8.3%) had an externalizing disorder. Externalizing psychiatric disorders were most commonly observed in the developmental and epileptic encephalopathies (29.4%) compared to other epilepsy groups. The most important factors associated with occurrence of internalizing psychiatric comorbidity was failure of at least two antiseizure medications, while intellectual and developmental delay was the most important associated factor with externalizing psychiatric comorbidity.

Conclusion: Psychiatric disorders was probably underdiagnosed and undertreated in this population. These disorders should be investigated particularly in children with poor seizure control or presenting with intellectual and developmental delay.

Keywords: internalizing psychiatric disorders, externalizing psychiatric disorders, intellectual and developmental delay, comorbidity, childhood epilepsy.

V.3. **Introduction**

Epilepsy is increasingly recognized as a spectrum disorder not only manifested by the occurrence of epileptic seizures, but also by a wide range of neurological, cognitive and psychiatric disorders that increase the disease burden (1). Psychiatric disorders are up to 5 times higher in children with epilepsy compared to the general population (2). Epidemiological studies on the prevalence of psychopathology in pediatric epilepsy have reported an estimated overall risk of 21 to 60% (3). These disorders increase the disease burden, compromise the quality of life for both the child and the family, and are associated with an increased risk of suicidality (4,5). Psychiatric disorders may be divided into internalizing symptoms referring to inner-directed problems that cause internal psychological distress, such as anxiety and depression, or externalizing symptoms referring to outer-directed problems that bother other individuals and cause interpersonal conflict in the external environment, such as impulsivity, hyperactivity, and aggressive behavior (6).

While seizures can result in psychiatric comorbidity, data from epidemiological studies have established a “bidirectional” relationship between psychiatric disorders and epilepsy, whereby one disorder can lead to the other and there exists a common pathogenic mechanism in the brain operant for both disorders (7,8). Several risk factors have also been identified for the development of psychiatric comorbidity in children with epilepsy, including psychosocial factors, such as family relationship satisfaction (9), family stress (10) socio-economic status (11), polytherapy (4,10), higher seizure frequency (12), and concomitant neurodevelopmental disorders (13).

Recognition and management of psychiatric comorbidities at the time of child’s initial evaluation is indispensable as part of a comprehensive epilepsy care plan (7). Identification of risk factors for these comorbidities may also help clinicians identify children at risk of developing these disorders early on. Unfortunately, psychiatric disorders in children with epilepsy are not well described in developing countries, and most studies on the factors associated to these disorders were conducted in developed countries. This study attempts to evaluate the prevalence of psychiatric disorders and associated factors in a large cohort of children with epilepsy in Lebanon.

V.4. **Materials and Methods**

V.4.1. Study design, setting, and population

A medical record analysis was conducted of the children with new onset seizures cohort identified at the American University of Beirut Medical Center (AUBMC). This study is a collaborative effort of multiple neurologists and pediatric neurologists from all 6 governorates of Lebanon, who have been referring patients with new onset seizures to AUBMC were a full clinical evaluation and work-up is performed. The work-up includes a detailed history and description of seizures, a 3-hour sleep deprived EEG, physical and neurological examinations, and a 3-hour sleep deprived brain MRI.

This study included newly diagnosed children with epilepsy recruited between 2010 and 2016 and who were initiated on anti-seizure medications (ASMs) for management of seizures. These children have been closely followed up for a period ranging between 2 to 11 years after diagnosis, through scheduled clinic visits or telephone consultations. This study excluded children with severe intellectual and developmental delay (IDD) because it is difficult to detect psychiatric disorders in these patients, given that they do not have the skills needed to report or describe their emotions, requiring clinicians with specialized expertise in diagnosing psychiatric disorders in patients with cognitive disability and using specially designed scales (14). We also excluded children who were younger than 5 years at last follow-up because it was considered the minimal age at which psychiatric disorders may be apparent in children.

V.4.2. Ethical approval

This study was approved by the Institutional Review Board of the AUBMC, and all children enrolled in this study had an informed consent signed by one of their parents.

V.4.3. Assessment of psychiatric disorders

The presence of any psychiatric disorders was assessed by reviewing the accumulated medical record throughout the follow-up period. Psychiatric disorders were considered to be present if the child was referred to a pediatric psychiatrist, psychologist, behavioral or cognitive therapist, or neurologist and diagnosed with a psychiatric disorder according to the DSM-5 criteria, or if the medical record provided clear evidence of taking a medication for a psychiatric disorder. Psychiatric side effects resulting from ASM use were not included in the analysis. This was identified by the treating physician when a psychiatric illness was attributed to taking an ASM known to be associated to psychiatric side effects such as levetiracetam, perampanel, zonisamide, and topiramate. Psychiatric disorders were divided into internalizing disorders and externalizing disorders according to the DSM-55 criteria (6). Externalizing disorders include attention Deficit hyperactive disorder (ADHD),

oppositional defiant disorder, and conduct disorder. Internalizing disorders include generalized anxiety disorder, social phobia, separation anxiety, panic disorder, obsessive–compulsive disorder, agoraphobia, post-traumatic stress disorder, major depressive disorder, dysthymic disorder, mania, and hypomania.

V.4.4. Assessment of Intellectual and Developmental Delay

All patients underwent an assessment to evaluate for the presence and severity of Intellectual and Developmental Delay (IDD). Children younger than 6 years of age were evaluated using the Denver Development Screening Test (15). Older children were assessed according to the Diagnostic and Statistical Manual of Mental Disorders criteria, which classifies intellectual delay as mild, moderate, severe, or profound based on deficits in intellectual functioning as well as difficulties in conceptual, social, and practical areas of living (6). For example, children with mild intellectual delay may struggle with learning abilities and exhibit immaturity in social interactions, with communication and language skills that are more concrete than expected for their age. Children with moderate intellectual delay display marked limitations compared to their peers, with significant differences in social and communicative behavior. However, children with mild and moderate intellectual delay can still care for their personal needs, including eating, dressing and hygiene. Children with severe and profound intellectual delay have limited or very limited language development and have substantial limitations in the conceptual domains. They require support or are completely dependent on others for all activities of daily living (6). For the purpose of our analysis, we combined children with severe and profound delays into a single category, and included three groups of IDD (mild, moderate, or severe). To ensure the accuracy and consistency of the assessments, research fellows with specialized training in administering these tests were responsible for conducting the evaluation and scoring the degree of deficit. These chosen assessment tools were selected based on factors such as feasibility in terms of cost, accessibility, time requirements, and training considerations.

V.4.5. Sleep deprived Electroencephalogram (EEG) and classification of EEG findings

The EEGs were recorded on digital Nicolet machines (Natus^{R} Neurodiagnostics) with electrodes placed according to the International 10-20 system. At the initial visit, a 3-hour sleep deprived video-EEG with sleep recording was recorded from all patients. At each follow-up visit, a 60-minute sleep deprived EEG recording was performed. The EEG obtained at the initial visit were stratified according to the presence or absence of interictal epileptiform discharges (IEDs). Focal IEDs were classified based on their topography, morphology and presence or absence of focal slowing into focal maturational or focal non-maturational discharges (16). The generalized spike wave discharges (GSWD) of the type seen in patients with a genetic

generalized epilepsy (frequency of more than 2.5 Hz associated with a normal background) were labeled as idiopathic generalized discharges (16). The GSWD of the type seen in patients with a developmental and epileptic encephalopathy (frequency of less than 2.5 Hz associated with a slow and disorganized background with or without concomitant focal or multifocal IEDs) were labelled as symptomatic generalized discharges.

V.4.6. Brain MRI and classification of neuro-imaging findings

Brain MRIs were obtained from a 1.5 or 3T scanner (Ingenia; Phillips Healthcare) using an imaging-acquisition protocol that included 3D T1 (1 mm slice thickness) and 3D fast fluid-attenuated inversion recovery (FLAIR; 0.9- or 1-mm slice thickness) of the whole brain with multiplanar reconstruction, axial and coronal inversion recovery (2 mm slice thickness), axial T2 TSE and T2 FFE (4 mm slide thickness) and axial diffusion weighted images (4-5 mm slice thickness). The 3D images were obtained with no interslice gap. MRI findings were classified as epileptogenic or non-epileptogenic based on previously published criteria (17–19). MRI abnormalities consisting of isolated subcortical lesions or abnormal signal, nonspecific white matter hyperintensities, hydrocephalus, and brain atrophy were considered incidental findings.

V.4.7. Seizure types and epilepsy syndromes classification

Seizure types were classified according to the latest ILAE 2017 classification of seizure types (20). The case report file of each child was entirely reviewed at last follow-up to ensure that the correct electroclinical syndrome was made. The electroclinical syndromes were classified according to the latest International League Against Epilepsy (ILAE) classification of the epilepsies (21) and the recent ILAE classification and definition of epilepsy syndromes (22).

V.4.8. Statistical Analysis

Descriptive results were reported as percentages for qualitative variables and mean, median and range for quantitative variables. Cross tabs with Chi-square test were done for some variables vs. internalizing/externalizing psychiatric disorders. Univariable logistic analysis was conducted to identify factors associated to internalizing/externalizing psychiatric disorders. Variable significant in univariable analysis were entered into the multiple logistic regression to identify independent factors associated with these disorders. Level of significance was set at 0.05 level. All analysis was performed on SPSS.

V.5. **Results**

V.5.1. Clinical characteristic of the study population

The original cohort consisted of 694 children, of whom 126 were excluded from evaluation for psychiatric comorbidity either because they were younger than 5 years at last follow-up or had severe IDD.

338 (59.5%) were males and the mean age at seizure onset was 6.9 years (SD=4.97) (table 1). The duration of follow-up ranged between 2 and 12.4 years and had a median of 7.4 years (interquartile range: 5.8-9.0). The majority of children presented with 1 to 5 seizures prior to treatment (58.1%) and had only a single seizure type throughout follow-up (68%). Focal impaired awareness seizures were the most common seizure type throughout follow-up (42.6%), followed by focal to bilateral tonic-clonic seizures (33.8%).

Interictal epileptiform discharges on EEG were seen in 75.9% of children. 118 children (21.1%) presented with an epileptogenic lesion on brain MRI and 72 children (12.7%) had IDD. One or more psychiatric comorbidity was reported in 75 children (13.2%), with 30 having an internalizing disorder, and 47 having an externalizing disorder.

Table 1 Clinical characteristics of the study cohort (N=568) evaluated for psychiatric comorbidity

Variable	**Mean ±STD**	**Range**	**Median (IQR)**
Duration of follow-up (years)	7.2±2.3	2-12.43	7.4 (5.8-9.0)
Variable		N (%)	
Gender			
Male		338 (59.5)	
Female		230 (40.5)	
Monthly income (N=555)*			
<500$		132 (23.8)	
<1000$		191 (34.4)	
1000-3000$		190 (34.2)	
>3000$		42 (7.6)	
Age at onset of epilepsy			
Less than 2		73 (12.9)	
2 to 5		100 (17.6)	
5 to 10		177 (31.2)	
More than 10		218 (38.4)	
Seizure types throughout follow-up			
Focal impaired awareness seizures		242 (42.6)	
Focal to bilateral tonic-clonic seizures		192 (33.8)	
Focal aware seizures		99 (17.4)	
Generalized onset tonic-clonic seizures		86 (15.1)	

Absence seizures	83 (14.6)
Myoclonic jerks	48 (8.5)
Epileptic Spasms	13 (2.3)
Other**	16 (2.8)
Number of seizure throughout follow-up	
1 type	386 (68)
2 types	152 (26.8)
3 types or more	30 (5.3)
Pretreatment number of seizures	
1-5	330 (58.1)
6-10	33 (5.8)
11-100	47 (8.3)
≥100	158 (27.8)
Presence of epilepsy risk factors	
Yes	363 (63.9)
No	205 (36.1)
Intellectual and developmental delay	
Yes	72 (12.7)
No	496 (87.3)
IEDs on initial or subsequent EEG	
Yes	431 (75.9)
No	137 (24.1)
Epileptogenic Lesion on MRI (N= 561)* **	
Yes	118 (21.1)
No	443 (78.9)
Epilepsy classification	
Self-limited focal epilepsies	120 (21.1)
Genetic generalized Epilepsies	153 (26.9)
Focal non-maturational epilepsy	275 (48.4)
Developmental and epileptic encephalopathies	20 (3.5)
Failed at least two ASMs	
Yes	104 (18.3)
Presence of a psychiatric disorder	
No	493 (86.8)
Any psychiatric disorder	75 (13.2)
Internalizing psychiatric disorder	30 (5.3)
Externalizing psychiatric disorder	47 (8.3)

*monthly income was collected from the parents at the time of study recruitment, 13 participants didn't respond to this question.
**Other seizure types include eyelid myoclonia in 8 children (1.4%), myoclonic absence in 3 (0.5%), myoclonic atonic seizures in 2 (0.45%), atonic seizures in 2 (0.4%), and tonic seizures in 1 child (0.2%).
*** 7 children didn't have an MRI done.

V.5.2. Psychiatric disorders in different epilepsy syndromes and association with intellectual and developmental delay

Concerning specific epilepsy syndromes, 120 children (21.1%) had a self-limited focal epilepsy, 153 (26.9%) had a genetic generalized epilepsy, 275 (48.4%) had a focal non-maturational epilepsy, and 20 (3.5%) had a developmental and epileptic encephalopathy (DEE). Externalizing psychiatric disorders were most commonly observed in the group having DEEs (29.4%), followed SeLFEs and the focal non-maturational epilepsy group (7.5% and 73% respectively), and the GGEs (5.9%) (p=0.007). Conversely, the percentages of internalizing disorders within different epilepsy groups did not significantly differ (p=0.825) (table 2).

Externalizing disorders were also more common in children with IDD (21.7%) compared to those with no IDD (5.6%) (p<0.001). This difference however was not observed for the internalizing disorders (p=0.444).

Table 2 Psychiatric disorders in different epilepsy syndromes and association with Intellectual/ developmental delay

	Externalizing psychiatric disorder			**Internalizing psychiatric disorder**		
	no	yes	P value	no	yes	P value
Epilepsy classification						
SeLFE	111 (94.1)	9 (7.5)		115 (95.8)	5 (4.2)	
GGE	144 (94.1)	9 (5.9)		146 (95.4)	7 (4.6)	
Focal non-maturational epilepsy	255 (92.7)	20 (7.3)	**0.007**	258 (93.8)	17 (6.2)	0.825
DEE	12 (70.6)	5 (29.4)		16 (94.1)	1 (5.9)	
Intellectual and developmental delay						
No	468 (94.4)	28 (5.6)	**<0.001**	471 (95)	25 (5)	0.444
yes	54 (78.3)	15 (21.7)		64 (92.8)	5 (7.2)	

V.5.3. Associations between clinical factors and psychiatric disorders

Different associations were found for internalizing and externalizing psychiatric disorders when analyzed separately. There was no significant association between gender or monthly income and having internalizing or externalizing disorders.

Univariable analysis of associations with internalizing psychiatric disorders showed that experiencing 3 or more seizure types (p=0.01) and failure of at least two ASMs to control seizures (p=0.033) were associated with a higher probability of developing these disorders. On multivariable analysis, experiencing 3 seizure types or more was no longer significantly associated with internalizing disorders, but rather the most important factor was a failure of at least two ASMs to achieve seizure control (p=0.016, OR 2.9, CI 1.2-6.9). Older age at seizure also showed an association with internalizing psychiatric disorders of moderate significance (p=0.076, odds ratio OR 3.9, confidence interval CI 0.9-17.8) (table 3).

Factors associated with externalizing disorders in univariable analysis were younger age at seizure onset (p <0.001), experiencing epileptic spams (p <0.001), having a greater number of pretreatment seizures (p=0.015), presence of epileptiform discharges on EEG (p=0.03), detection of an epileptogenic lesion on brain MRI (p=0.025), having IDD (p <0.001), and being diagnosed with a DEE (p <0.001). On multivariable analysis, only having IDD was significantly associated with having an externalizing disorder (p=0.006, OR 3.19, CI 1.4-7.3) (table 4). Interestingly, failure of at least 2 ASMs to achieve seizure control showed no significant association with externalizing disorders.

Table 3 Associations between demographic and clinical factors and internalizing psychiatric disorders in a cohort of children with epilepsy.

	Internalizing psychiatric disorders			
Factor	p-value	Crude OR (95% CI)	p-value	Adjusted OR (95%CI)
Gender	0.955	0.97 (0.46-2.05)		
Monthly income				
<500$	Ref			
<1000$	0.861	1.09 (0.41-2.89)		
1000-3000$	0.648	0.78 (0.27-2.22)		
>3000$	0.334	1.88 (0.52-6.76)		
Age at onset of epilepsy				
Less than 2	Ref			
2 to 5	0.997	0	0.996	0
5 to 10	0.518	1.68 (0.34-8.11)	0.516	1.69 (0.34-8.28)
More than 10	0.091	3.58 (0.81-15.73)	0.076	3.93 (0.88-17.85)
Seizure types				
GOTC	0.811	1.12 (0.41-3.01)		
Absence	0.829	0.89 (0.30-2.61)		
Myoclonic Jerks	0.334	1.71 (0.57-5.14)		
Spams	0.999	0		
Tonic	1	0		
Atonic	0.999	0		
FAS	0.392	1.47 (0.61-3.52)		
FIAS	0.236	1.56 (0.75-3.27)		
FBTC	0.75	1.13 (0.53-2.43)		
Number of seizure types				
1 type	Ref		Ref	
2 types	0.977	0.99 (0.40-2.41)	0.565	0.76 (0.30-1.92)
3 types or more	**0.010**	4.10 (1.40-11.93)	0.106	2.63 (0.82-5.51)
Pretreatment number of seizures				
1-5	Ref			
6-10	0.998	0		
11-100	0.353	1.71 (0.55-5.33)		
≥100	0.802	1.11 (0.49-2.55)		
IEDs on EEG	0.229	0.62 (0.28-1.36)		
Epileptogenic Lesion on MRI	0.220	1.66 (0.73-3.72)		
Intellectual and developmental delay	0.502	1.41 (0.52-3.79)		
Presence of epilepsy Risk factors	0.219	0.62 (0.29-1.31)		
Epilepsy Syndrome				
GGE	Ref			
SeLFE	0.870	0.91 (0.28-2.93)		
Focal non-maturational epilepsy	0.490	1.37 (0.56-3.39)		
DEE	0.932	1.01 (0.13-9.42)		
Failed at least two ASMs	**0.033**	2.36 (1.07-5.21)	**0.016**	2.91 (1.22-6.98)

OR: odds ratio; CI: confidence interval; GOTC: generalized-onset tonic clonic; FAS: focal aware seizures; FIAS: focal impaired awareness seizures; FBTC: focal to bilateral tonic clonic seizures; IEDs: interictal epileptiform discharges; EEG: electroencephalogram; MRI: magnetic resonance imaging; ASMs: antiseizure medications.

Table 4 Associations between demographic and clinical factors and externalizing psychiatric disorders in a cohort of children with epilepsy.

	Externalizing psychiatric disorders			
Factor	p-value	Crude OR (95% CI)	p-value	Adjusted OR (95%CI)
Gender	0.348	0.74 (0.39-1.38)		
Monthly income				
<500$	Ref			
<1000$	0.347	0.67 (0.29-1.54)		
1000-3000$	0.578	0.79 (0.35-1.78)		
>3000$	0.933	1.05 (0.32-3.46)		
Age at onset of epilepsy				
Less than 2	Ref		Ref	
2 to 5	0.600	0.79 (0.34-1.86)	0.454	1.49 (0.52-4.23)
5 to 10	0.091	0.49 (0.22-1.12)	0.700	1.23 (0.43-3.57)
More than 10	**<0.001**	0.15 (0.05-0.41)	0.189	0.44 (0.13-1.51)
Seizure types				
GOTC	0.372	0.71 (0.27-1.87)		
Absence	0.423	0.75 (0.28-1.96)		
Myoclonic Jerks	0.989	1.01 (0.35-2.94)		
Spams	**<0.001**	21.17 (6.61-67.78)	0.246	3.47 (0.42-28.45)
Tonic	1	0		
Atonic	0.999	0		
FIAS	0.361	1.32 (0.72-2.40)		
FBTC	0.354	0.73 (0.37-1.42)		
Number of seizure types				
1 type	ref			
2 types	0.921	0.97 (0.47-2.0)		
3 types or more	0.845	0.95 (0.22-4.22)		
Pretreatment number of seizures				
1-5	Ref		Ref	
6-10	0.499	1.55 (0.44-5.52)	0.539	1.51 (0.41-5.65)
11-100	0.522	1.44 (0.47-4.42)	0.864	1.11 (0.34-3.58)
≥100	**0.015**	2.25 (1.17-4.31)	0.406	1.58 (0.53-4.72)
IEDs on EEG	**0.030**	2.85 (1.11-7.35)	0.257	1.86 (0.63-5.46)
Epileptogenic Lesion on MRI	**0.025**	2.08 (1.10-3.96)	0.631	1.25 (0.51-3.05)
Intellectual and developmental delay	**<0.001**	5.37 (2.79-10.30)	**0.006**	3.19 (1.40-7.28)
Presence of epilepsy Risk factors	0.349	1.36 (0.71-2.61)		
Epilepsy Syndrome				
GGE	Ref		Ref	
SeLFE	0.594	1.30 (0.50-3.38)	0.544	1.52 (0.39-5.93)
Focal non-maturational epilepsy	0.584	1.25 (0.56-2.83)	0.752	1.23 (0.34-4.51)
DEE	**<0.001**	13.09(4.32-39.67)	0.434	2.18 (0.31-15.31)
Failed at least two ASMs	0.877	1.06 (0.49-2.27)		

OR: odds ratio; CI: confidence interval; GOTC: generalized-onset tonic clonic; FAS: focal aware seizures; FIAS: focal impaired awareness seizures; FBTC: focal to bilateral tonic clonic seizures; IEDs: interictal epileptiform discharges; EEG: electroencephalogram; MRI: magnetic resonance imaging; ASMs: antiseizure medications.

V.6. **Discussion**

This study evaluated the prevalence of psychiatric disorders in a cohort of children recruited at the time of seizure onset and followed up for a long duration of up to 12 years. It also assessed the factors associated to internalizing and externalizing psychiatric disorders separately, allowing identification of different factors within each group. In this study, 13% of children with epilepsy were diagnosed with a psychiatric disorder, among which 5.3% had and internalizing disorder and 8.3% had an externalizing disorder. This percentage is lower than the prevalence of psychiatric disorders ranging from 40 to 50% in previous studies (3). Psychiatric disorders were probably under-reported in this study because children were not routinely referred for psychiatric evaluation unless they showed obvious psychiatric symptoms as warranted by the caregiver. This pinpoints to the underdiagnoses of psychiatric comorbidities in children with epilepsy, perhaps particularly in developing countries, and the importance of screening for these comorbidities in routine clinic visits.

Externalizing psychiatric disorders were more common in children with DEEs than other epilepsy types; an expected finding since DEE syndromes are associated with neurodevelopmental impairment involving several aspects from cognition, attention, behavior, to sleep (23). This was further validated by the fact that the presence of IDD was the single most important factor associated to an externalizing disorders. Previous studies have also found that neurodevelopmental spectrum disorders were strongly correlated with externalizing disorders (13,24). This result is likely a reflection of experimental findings that reported neuroanatomic delay in regional cortical maturation leading to global delay in children with ADHD (25). By contrast, this study and others (13) found no association between internalizing disorders and IDD or epilepsy group. This finding however doesn't necessarily mean a lack of association and should be interpreted carefully, because internalizing disorders are more difficult to detect in children with IDD since they do not involve outward manifestations, thus they may be less apparent, and the child may lack the verbal skills needed to communicate his emotions.

The literature has yielded conflicting results regarding the association between age at seizure onset and externalizing disorders. While younger age at seizure onset was reported as a risk factor for ADHD; an externalizing disorder (26), this study and others (13,27) found no significant association. Younger age at seizure onset showed a significant association in univariable analysis, however it didn't reach statistical significance in multivariable analysis. This association is not surprising since DEEs which are accompanied by these disorders have an onset at early childhood. Conversely, an inverse association was found between age at onset and internalizing disorders, whereby older age at seizure onset increased the odds of having an internalizing disorders. This finding was also reported in a previous study (13), however, in this study it didn't reach statistical significance in multivariable analysis.

Although internalizing disorders are strongly associated with epilepsy, specific epilepsy related-factors such as age at seizure onset, seizure type or syndrome, seem to be less involved in the development of these disorders.

The single most important factor associated with internalizing psychiatric comorbidity in this study was pharmacoresistance, defined here as failure of at least two ASMs in achieving seizure control. Our findings are consistent with previously published studies (28–30), where depression, anxiety, and mood disorders were correlated with poor seizure control, increased seizure severity, and pharmacoresistance. These results reflect previous finding whereby depression was linked to hypothalamic-pituitary-adrenal axis activation and alterations in the balance of release and re-uptake of excitatory and inhibitory neurotransmitters which could increase the development of epileptic activity (31). Hippocampal volume reduction in depressed patients may also play a role in seizure worsening (32). Alternatively, failure to achieve seizure control may aggravate internalizing psychiatric symptoms due to its negative implications such as poor quality of life and stigma (33). Psychiatric comorbidities may also be associated with poor adherence to ASM treatment leading to poor seizure control (34).

Some studies have showed that belonging to a higher income group was associated with significant psychopathology (35), while others found that belonging to a lower income group was associated with more psychopathology, such as depression or behavioral problems (36,37). Our study however showed no significant association between income and the development of internalizing or externalizing psychiatric disorders. This is likely because families of lower economic classes in Lebanon receive social support from extended family and non-profit organizations, and the economic burden is not necessarily perceived by the child.

The absence of a relationship between psychiatric comorbidity and gender in this study is also in line with previous studies in pediatric epilepsy (4,37,38). This is contrary to studies in the general population where mood or anxiety disorders were found to be more common in girls than boys (39). This trend which is not seen in pediatric epilepsy may point to the presence of other pathologic substrates responsible for psychiatric disorders in these patients.

As with other studies, this study has several limitations. A major limitation is the underestimation of psychiatric disorders in this sample because the children were not systematically screened for psychiatric comorbidity in routine clinic visits and were not routinely administered a scale for evaluation of these comorbidities, unless the child complained of psychiatric symptoms. In addition, psychiatric comorbidities were retrospectively identified from the medical records of the children. The duration of follow-up was variable and ranged from 2 to 12 years, which means children with shorter duration of follow-up may have developed psychiatric comorbidity later on. In addition, in children younger than 6 years of age, we relied on the Denver Development

Screening Test to assess for the presence and severity of IDD without confirmation from another assessment tool. The strengths of this study is the inclusion of a large sample size of children distributed over all governorates of Lebanon, thus our results are representative of children with epilepsy residing in that geographical area, and it is the first to evaluate psychiatric comorbidity in children with epilepsy in this region.

V.7. **Conclusion**

Psychiatric comorbidity may be under-reported in children and adolescents with epilepsy residing in developing countries. Clinicians are warranted to screen for psychiatric comorbidity in routine clinic visits, especially in children having signs of intellectual or developmental delay, and in patients with poor seizure control. Future research should systemically evaluate children and adolescents with seizures using validated scales to measure psychopathology, and reexamine its multifactorial associations, to develop evidence based interventional programs to mitigate the burden of these disorders.

V.8. **References**

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Chapter VI. General Discussion

Epilepsy is increasingly recognized as a spectrum disorder that is not limited to seizures but is also accompanied by a wide range of comorbidities. Management of epilepsy therefore requires a multidisciplinary approach focusing on all aspects of the disease. In clinical practice, it is important to predict early on after epilepsy diagnosis the likely clinical course of the disease, in terms of seizure control and drug resistance. This would provide parents with answers, and guide in therapeutic decision making with timely selection of surgical candidates. Children with poor seizure control also have a greater risk of experiencing a wide range of epilepsy comorbidities, such as intellectual disability, psychiatric disorders, and sudden unexpected death. It is of paramount importance to routinely monitor for these comorbidities especially in children with poor seizure control. Fortunately, providing appropriate treatment for seizures in a timely manner may prevent the development and progression of these comorbidities. This study aimed to evaluate predictors of treatment outcome and the factors associated to psychiatric comorbidity in a cohort of children with newly diagnosed epilepsy.

VI.1. **Main findings**

The first objective of this study was to determine early predictors of 2-year seizure remission obtained at baseline visit in children newly diagnosed with epilepsy. Our study showed that almost 80% of children with new-onset seizures are able to achieve a 2-year remission after treatment initiation. Epidemiological studies have also reported a high percentage of children attaining remission (43,91). Epilepsy can thus be regarded as a relatively benign condition with a good prognosis in the majority of children. Remission is usually achieved soon after diagnosis and ASM initiation (92–94). In this study, more than half of the children achieved seizure freedom within the first year following ASM initiation. Thus the outlook is good for most children except those presenting with alarming clinical variables.

While multiple studies have looked at the factors associated to poor seizure control (42,43,94,95), this study identified early clinical variables available at baseline, and was the first to perform a recursive analysis that allowed for a prioritization and splitting of those predictor variables. Multiple studies have linked the presence of IDD to poor seizure control (32,42,95). This study however found that the presence and severity of IDD was the most important baseline predictor variable pertaining to non-remission. The detection of an epileptogenic lesion on brain MRI has been reported as predictor of poor seizure control (43,94,96–98), however this study showed it was significant only in children with no evidence of IDD, clearly showing that IDD supersedes the detection of an epileptogenic lesion in the prediction model. The third predictor variable for non-remission was the pretreatment seizure number, which was significant in children with no evidence of IDD or epileptogenic lesion on MRI. This factor however

should be interpreted carefully, as the association between the number of pretreatment seizures and seizure remission was only significant for focal-onset seizures. This finding was also documented in a previous review (41). Thus children presenting with a high number of pretreatment focal seizures should be carefully observed even in the absence of IDD or an epileptogenic lesion on brain MRI.

The second objective of this study was to determine predictors of drug resistant epilepsy among different childhood epilepsy syndromes in this cohort. While multiple studies have looked at the determinants of drug resistance in childhood epilepsy (25,30,44,96), these studies tend to lump together all epilepsy types, and thus their results are skewed towards the epilepsy syndromes more prevalent within the population. Also, given the variabilities in clinical characteristics in different epilepsy syndromes, we expected that the predictors of DRE within different epilepsy groups would vary. In addition, most of these studies used different definitions of drug resistance, and were conducted before the ILAE published its consensus definition of drug resistant epilepsy (21). Large scale studies that prospectively identify patients with new-onset seizures and study their prognosis are also limited in number. This study was the first to identify predictors of DRE after classification into different childhood epilepsy groups. It is also among the few studies that have examined the development of pharmacoresistance prospectively from the time of initial diagnosis of epilepsy.

In this study, 29% of children met the definition of drug resistance. This percentage is in agreement with the pooled prevalence of DRE found in a meta-analysis (31). Childhood epilepsies were divided into 4 main subgroups: (1) SeLFEs, (2) GGEs, (3) focal non-maturational epilepsies, and (4) DEEs. Different associations between DRE and clinical variables were identified for the other three groups.

Within the GGEs, factors predictive of drug resistance were younger age at epilepsy onset, and experiencing multiple seizure types; specifically, GOTCs, myoclonus, and absence. This is in agreement with previous studies previous studies on JME (35), JAE (99), and CAE (99–101). Previous studies have also reported an association between younger age at seizure onset and DRE in GGEs (35,102) reflecting more severe brain dysfunction ensuing early on.

Within the focal non-maturational epilepsies, similar to GGEs, younger age at epilepsy onset and experiencing multiple seizure types were predictors of drug resistance. However distinct to GGEs, having an epileptogenic lesion on brain MRI and a greater number of pretreatment seizures also predicted DRE. This is in line with the results in study 1 where the presence of an epileptogenic lesion and having a great number of pretreatment seizures; particularly focal onset seizures, predicted poor seizure remission.

Within the DEEs, findings were rather different. Younger age at epilepsy onset was associated with a lower likelihood of DRE, probably reflecting patients with IESS who may have a better prognosis compared to other DEEs. This finding is concordant with a previous study that reported that having spasms as a sole seizure type predicts better prognosis in terms of seizure control (103). Experiencing specific seizure types, namely tonic seizures and focal impaired awareness seizures predicted DRE in this group. This likely reflects progression into syndromes with unfavorable prognosis such as Lennox-Gastaut syndrome.

Although the presence and severity of IDD was the most important predictor of non-remission in study 1, IDD was not significantly associated with DRE within the DEEs, probably because almost all children within this group had some degree of delay. IDD was associated with DRE only in the focal non-maturational epilepsy group, however it didn't reach statistical significance in multivariable analysis. This is likely due to the presence of other important variables within this group, such as the presence of an epileptogenic lesion brain MRI or having a greater number of pretreatment seizures.

Understanding the predictors of seizure control is of paramount importance to predict disease prognosis and aid clinicians in decision making, however, a comprehensive epilepsy management plan is not complete without understanding and monitoring the wide range of epilepsy comorbidities. Consequently, the third objective of this study was to evaluate psychiatric comorbidity and its associated factors in this cohort.

Psychiatric disorders were categorized into either internalizing or externalizing disorders according to the DSM 5 criteria (104). Our study found different association with both types of disorders. Externalizing disorders, such as ADHD, were significantly more prevalent in children with DEEs. This is not a surprising finding since the epileptic encephalopathies are particularly prone to cognitive and psychological comorbidities (105,106). This finding was not found for internalizing psychiatric disorders, as the prevalence of internalizing disorders didn't significantly differ among different epilepsy groups. This however doesn't necessarily mean a lack of association, since internalizing disorders are more difficult to detect, given that they don't have outward manifestations. Children with intellectual or developmental delay such as that seen with the DEEs for example may not have the skills to communicate their emotions, leading to an under-reporting of internalizing disorders in this group.

The most important factor associated with externalizing disorders was the presence of IDD. This finding was previously reported in another study (107), suggesting that these two disorders commonly coexist. Data from multiple studies have also established a link between the process responsible for epileptogenesis, cognitive dysfunction, and the development of psychiatric disorders (108). Clinical evidence supports the existence of a bidirectional relationship between seizure disorder and cognitive and psychological comorbidities. Psychiatric disorders may precede seizure

onset and exert an intrinsic effect on the development of epilepsy. Alternatively, seizures themselves and the process of epileptogenesis may contribute to the cognitive and psychological disorders seen in epilepsy (62,64). It is also possible that these disorders may develop concurrently and independently as a result of the same pathological event, such as status epilepticus, brain trauma, stress, or an inflammatory disease) (109).

Our study found a clear association between poor seizure control and the development of internalizing psychiatric disorders, as failure of at least two ASMs to achieve seizure control (indicating pharmacoresistance) was the most important factor associated to these disorders. This link was also found in study 2, were a history of psychiatric disorders predicted the development of DRE in patients having a GGE. Data from several epidemiologic studies have suggested that psychiatric disorders may increase the risk of developing seizures (110,111), and may be associated to a poor response to ASM treatment (50,112). Noteworthy is that psychiatric disorders may also be a consequence of living with treatment resistant seizures leading to a compromised quality of life and social stigma (113). Future prospective studies are warranted to further elucidate the causal relationship between seizure control and the development of psychiatric comorbidity.

VI.2. **Implications for practice**

This study provides valuable insight on early clinical variables that can predict seizure remission, regardless of the electro-clinical syndrome diagnosis. The prognostic patterns of different childhood epilepsy syndromes have been widely established in the literature, however a syndrome diagnosis is usually difficult to ascertain at the time of seizure onset, because it requires follow-up EEGs and monitoring of seizure semiology (13). The importance of our model is its ability to predict seizure control based on clinical variables available at visit 1, consisting of the presence of intellectual and developmental delay, presence of an epileptogenic lesion on brain MRI and number of pretreatment seizures. We anticipate that this data will provide additional perspectives when counseling patients and their parents and will allow for a timely selection of children who might require close follow-up or be considered for early neurosurgical intervention.

Early identification of drug resistant epilepsy is also of paramount importance, since intractable seizures can have devastating effects on the child and family, and are associated with a wide range of comorbidities and increased risk of death (114,115). Early intervention may spare cognitive and developmental function, and limit epilepsy comorbidities (116,117). However, early intervention requires early recognition. This study was able to identify clinical variables predictive of drug resistance across different childhood epilepsy syndrome groups, allowing recognition of pharmacoresistance as soon as possible.

This study was also able to identify some clinical factors associated to psychiatric comorbidity in children with epilepsy, however, a great concern raised by the data was the lack of systematic screening for psychiatric disorders in this vulnerable group, manifested by the low prevalence of disorders in this cohort. This raises awareness to the importance of investigation of psychiatric comorbidity even in a busy outpatient clinic, using validated self-rating screening instruments. Use of these instruments would allow identification of patients suffering from psychiatric symptoms to be referred for neuropsychiatric evaluation. Medical students, residents, and fellows should also be taught about the importance of investigating the psychiatric history when taking the clinical history of an epileptic patient, especially with the growing evidence on its influence on seizure control and ASM choice.

VI.3. **Strengths and limitations**

The strengths of this study are the inclusion a large cohort of child who were newly diagnosed with epilepsy at the time of recruitment, and who were prospectively followed up for a long duration of up to 12 years. All children were seen by an epiletologist to confirm the diagnosis of epilepsy. During the follow-up period, the children underwent an extensive evaluation through clinic visits and phone consultations by a team of trained physicians. In addition, all children underwent a sleep-deprived 3-hour video recorded EEG and epilepsy protocol brain MRI at the time of seizure onset. Moreover, the study evaluated multiple variables and confounders that might impact prognosis, which allowed for a comprehensive evaluation of the outcomes. In addition, seizures types and epilepsies were classified according to the ILAE latest guidelines, providing a standardized and reliable classification system.

This research study was a collaborative effort involving several hospitals with centralized monitoring at the AUBMC, with the aim of recruiting a larger sample size from across Lebanon. We do not believe our study had a selection bias since children from all governorates of Lebanon participated in this study and the distribution of patients included in this study closely mirrored the geographical distribution of the population across Lebanon's six administrative governorates. Specifically, within our study cohort, 16% of the children resided in the Beirut governorate, 32% in Mount Lebanon, 23% in North Lebanon, 13% in the Bekaa, and 16% in South Lebanon and Nabatieh. This indicates that the study sample is representative of the Lebanese population, allowing for the generalizability of the study's findings to the broader population in the region.

Attrition bias, whereby patients who are lost to follow-up are systematically different from those who continue in the study, was evaluated by examining if there were any significant differences between the excluded and included children for various relevant variables. The analysis revealed no significant differences in terms of clinical variables, including the presence of an epileptogenic lesion on brain MRI (p=0.83), the presence

and severity of intellectual and developmental disabilities (IDD) (p=0.12), and the number of seizures before treatment (p=0.78). These findings suggest that attrition bias was limited in this study, and the exclusion of these patients is unlikely to have introduced substantial bias into the results of this study.

As with any study, this study had several limitations. The duration of follow-up had a minimum of two years and ranged from two to twelve years. This may have introduced an information bias whereby the study outcomes (two-year remission, drug resistance, and psychiatric comorbidity) may have been underestimated in children with shorter duration of follow-up. In addition, some children were evaluated with a 1.5 Tesla MRI instead of a 3 Tesla MRI, which has a lower capacity of detecting lesions, thus a miss-classification bias may have occurred in classifying children having an epileptogenic lesion on brain MRI and those not. This would have been avoidable by the use of the same instrumentation for MRI.

Another source of information bias is the use of the Denver Development Screening Test to assess for the presence and severity of IDD without confirmation from another assessment tool in children below the age of 6 years. This screening tool was chosen due to its suitability for capturing both developmental and cognitive functioning in children with delays, as well as those who are too young to participate in more standardized testing methods. Evaluation of children by a neuropsychiatrist using a valid assessment tool would have yielded better results in the assessment of IDD.

This study required evaluation of adherence to treatment, since children who were non-adherent to treatment were excluded from the final analysis. For children receiving valproate, carbamazepine, phenytoin or phenobarbital, routine monitoring of serum levels for these medications was conducted. However, serum levels of newer ASMs were not routinely obtained due to the unavailability of local facilities and the high associated costs involved. For these drugs, adherence was recorded through inquiries made to the caregiver/patient regarding the administration of ASM as prescribed, which may have introduced a recall bias.

A source of confounding bias in this study was the lack of systematic genetic testing and non-inclusion of this variable in the statistical model. A large number of genes implicated in drug resistant epilepsy have been discovered, particularly in epileptic encephalopathies (118,119). Incorporation of genetic testing within the prediction model would likely contribute valuable information in predicting seizure control.

Another major limitation in assessing psychiatric comorbidity was the fact that this variable was retrospectively evaluated from the accumulated medical record of the child. If this variable had been evaluated prospectively using a validated screening tool and later by neuropsychiatric evaluation, we expect the frequency of psychiatric comorbidity to be higher than the one reported in this study.

We must also note the impact of covid-19 on research within the past 3 years, whereby clinic visits were limited, and some patients wouldn't attend to their scheduled EEG appointments. This may have influenced the quality of data collected during that period.

Chapter VII. Conclusion and future perspective

Our findings indicate that seizure control can be determined, to a large extent, by clinical variables obtained at baseline. This allows early identification of patients at risk of having poor seizure control early on after diagnosis, in order to refer them to a comprehensive epilepsy care center or evaluate their surgical candidacy. Predictors of drug resistance will vary among different epilepsy syndrome groups, given the variability in their clinical characteristics. Some clinical variables which are relevant in a certain group of epilepsies may not be relevant to the other. Our study allowed the identification of separate variables in different epilepsy groups, aiding clinicians in decision making and selecting patients likely to be drug resistant. This study was also able to identify a possible gap in the diagnosis and treatment of epilepsy comorbidities in Lebanon. Management of epilepsy is not limited to achieving seizure control, since early deficits in neuronal activity and connectivity contribute to a developmental cascade affecting different interacting brain regions, leading to neurodevelopmental and psychiatric disorders. As such, these disorders should also be therapeutic targets.

VII.1. **Research perspective**

One of the key factors highlighted in this study was the presence of an epileptogenic lesion on brain MRI and its association with poor outcome. Future studies will aim to stratify children with structural focal epilepsies per etiology, in order to identify the relationship between the nature of the lesion and drug resistance.

Moreover, since drug resistance is a dynamic process, and children who meet the definition for drug resistance may achieve seizure control later on, we aim to evaluate the long term outlook for children who met the definition of drug resistance, by determining whether remission after drug resistance is a realizable goal. An assessment of outcome after further treatment trials would give valuable insight and allow testing of the ILAE definition for drug resistance.

Future studies should also systematically investigate epilepsy comorbidities using validated tools. interventional programs targeting both clinicians and caregivers should be implemented to raise awareness about the importance of the management of these comorbidities in addition to seizure control. Arabic self-reported psychiatric comorbidity screening tools should also be validated for use in routine clinical practice in the region, allowing for early screening of these comorbidities in routine clinic visits. This is especially important in a busy clinic scenario.

Another important aspect in the management of epilepsy in children is the assessment of quality of life. Epilepsy is associated with disease-specific restrictions in physical activities and self-sufficiency, and it negatively impacts cognition and behavior. It also associated with stigma and increased depression scores. All of these

factors lead to a reduced quality of life in children with epilepsy. Data on the quality of life of children living with epilepsy in Lebanon is lacking. This important aspect should be assessed using validated epilepsy-specific quality of life measures, and its correlation with seizure severity, ASM side effects, and other clinical variables should be evaluated.

Another critical aspect in managing epilepsy effectively is adherence to antiseizure medications. Poor adherence to prescribed medication is considered to be the main reason of treatment failure for epilepsy, and is associated with increased morbidity and mortality, reduced quality of life, and increased health care costs. However, adherence can be challenging, particularly in pediatric patients, due to factors such as the taste of the medication, the need for multiple daily doses, or potential side effects. This problem is further complicated in developing countries such as Lebanon by an ongoing economic and political crises. Access to treatment has been facing enormous barriers the past 3 years, exacerbating the challenges in providing adequate medications. The absence of a comprehensive health insurance system further compounds the issue, leaving a large segment of the population without adequate coverage. These barriers to access to treatment create a distressing situation for parents with children with epilepsy, and may lead to poor adherence to treatment and poor seizure control. This situation underscores the need to evaluate adherence to ASMs in children with epilepsy in Lebanon, given the multifactorial challenges they may face in access to treatment.

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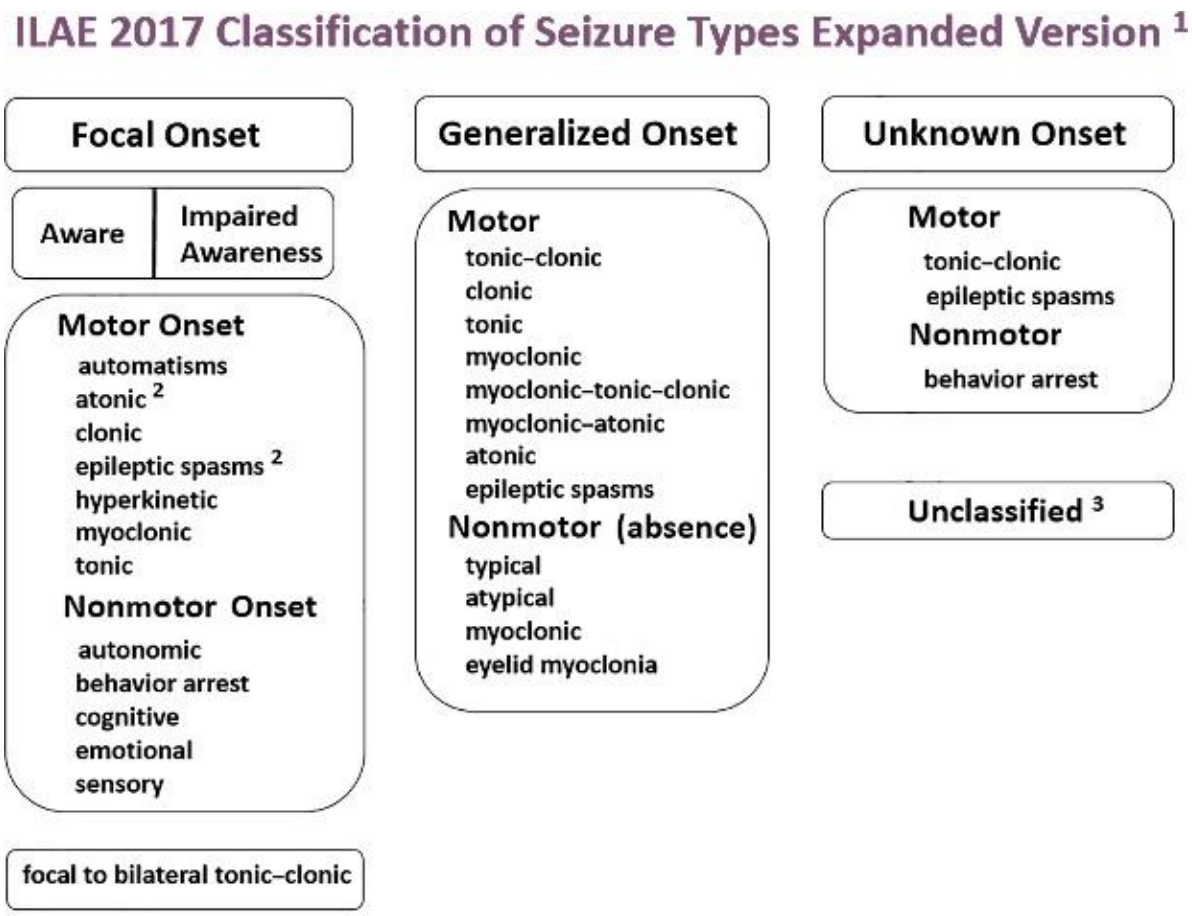
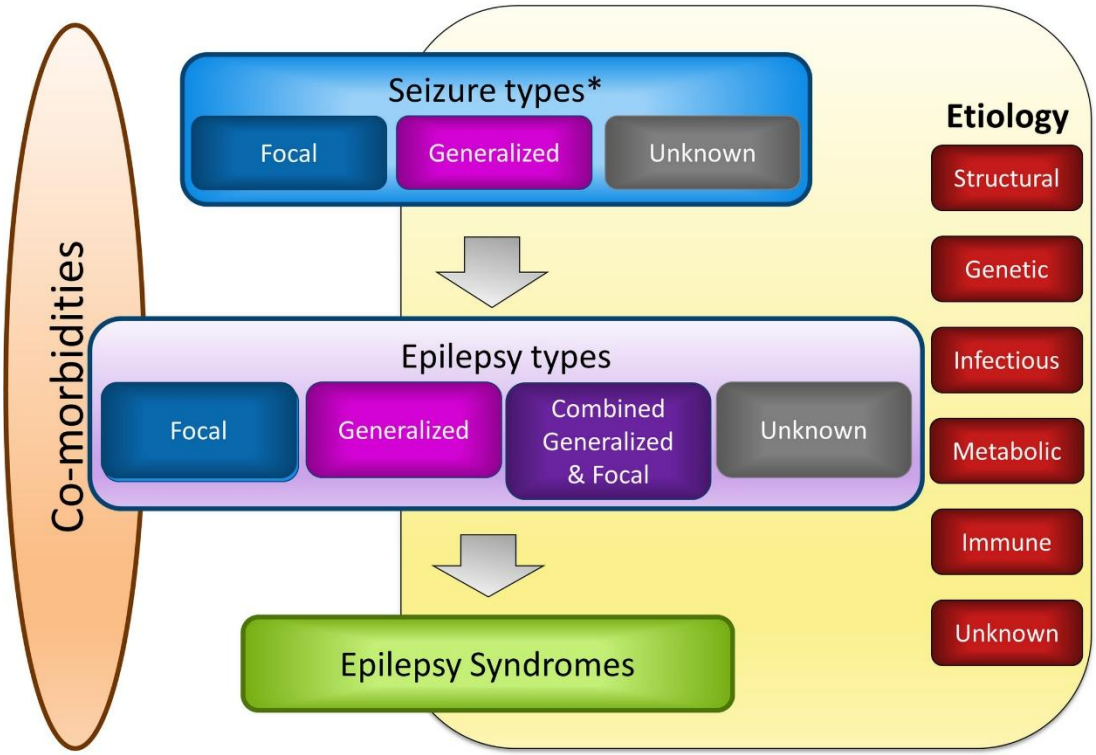
Appendices

Appendix 1. The expanded ILAE 2017 operational classification of seizure types.



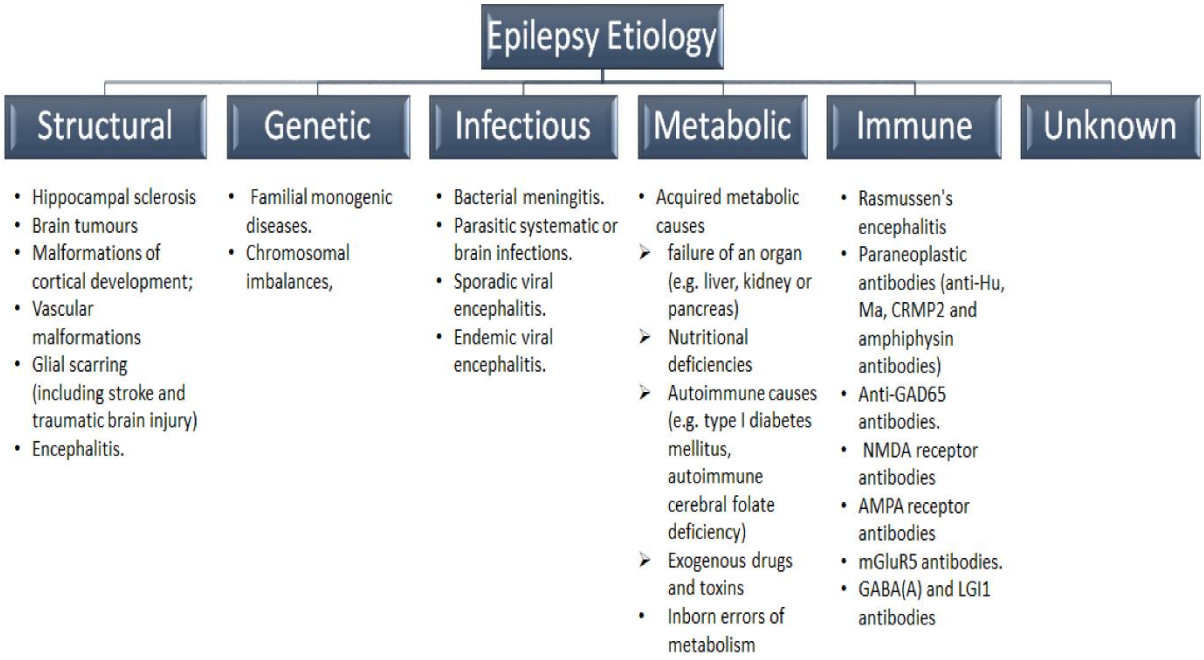
Fisher, R.S., Cross, J.H., French, J.A., Higurashi, N., Hirsch, E., Jansen, F.E., Lagae, L., Moshé, S.L., Peltola, J., Roulet Perez, E., Scheffer, I.E. and Zuberi, S.M. (2017), Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia, 58: 522-530. https://doi-org.ezproxy.unilim.fr/10.1111/epi.13670

Appendix 2. ILAE 2017 framework for classification of the epilepsies.



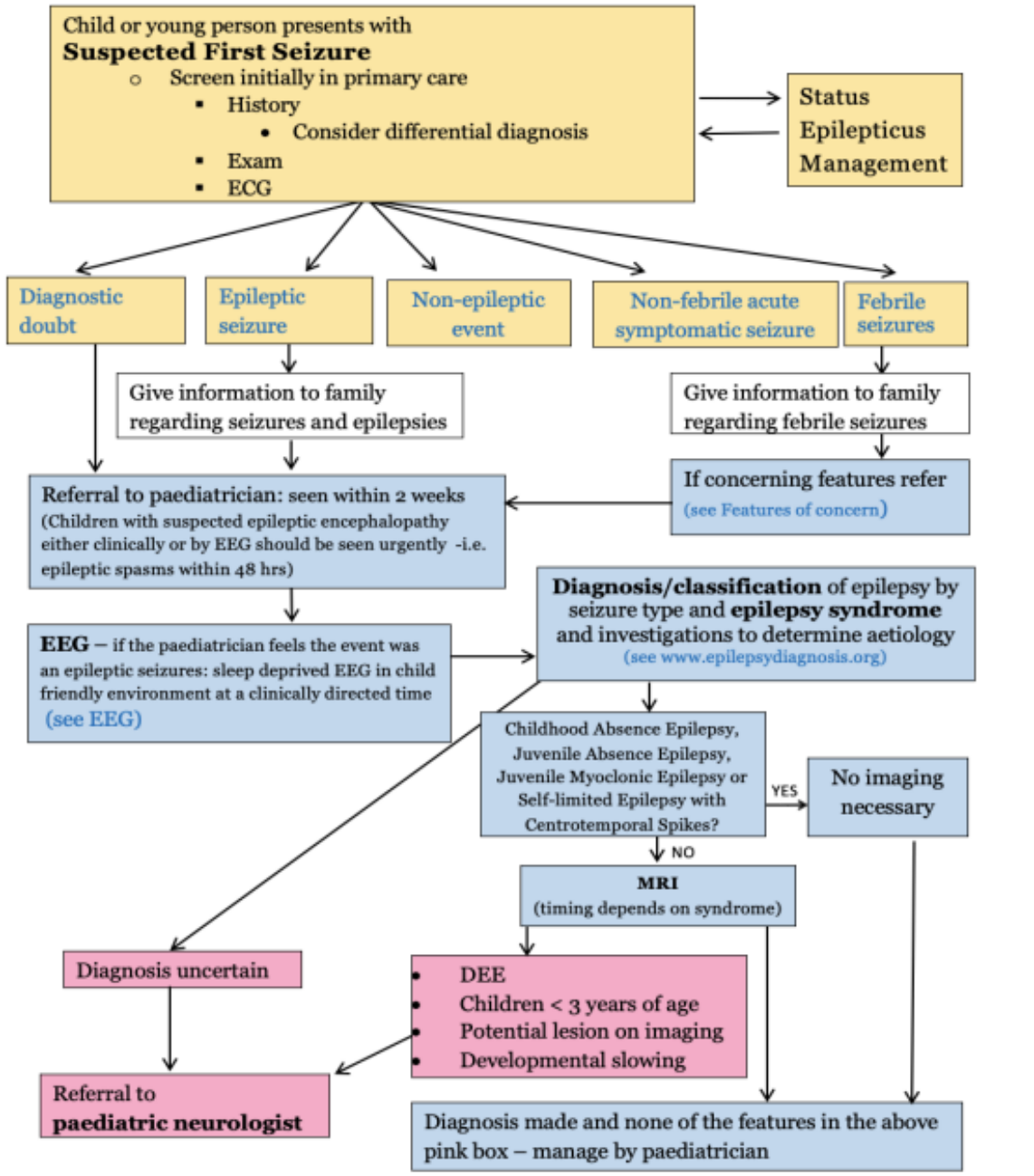
Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017 Apr;58(4):512–21.

Appendix 3. Etiology of epilepsies



Fan, H.-C.; Chiang, K.-L.; Chang, K.-H.; Chen, C.-M.; Tsai, J.-D. Epilepsy and Attention Deficit Hyperactivity Disorder: Connection, Chance, and Challenges. *Int. J. Mol. Sci.* **2023**, *24*, 5270. https://doi.org/10.3390/ijms24065270

Appendix 4. Epilepsy diagnosis and management flowchart



Note: Items in yellow boxes are generally initially performed by ED physicians, registered medical officers (RMOs) and general practitioners; items in blue boxes are generally performed by paediatricians; the pink boxes relate to paediatric neurology referral.
DEE: Developmental and epileptic encephalopathy

Paediatric Neurology Network Epilepsy Guidelines- Updated September 2022

Appendix 5. NICE 2022 treatment guidelines for treating specific seizure types

Seizure type	first-line monotherapy	second-line monotherapy	first-line add-on treatment	second-line add-on treatment	third-line add-on treatment	May exacerbate seizure type
Generalised tonic-clonic seizures	sodium valproate (except in women and girls able to have children) lamotrigine levetiracetam	lamotrigine levetiracetam	clobazam lamotrigine levetiracetam perampanel sodium valproate (except in women and girls able to have children) topiramate	brivaracetam lacosamide phenobarbital primidone zonisamide		
Focal seizures with or without evolution to bilateral tonic-clonic seizures	lamotrigine levetiracetam	carbamazepine oxcarbazepine zonisamide	carbamazepine lacosamide lamotrigine levetiracetam oxcarbazepine topiramate zonisamide	brivaracetam cenobamate eslicarbazepine acetate perampanel pregabalin sodium valproate (except in women and girls able to have children)	phenobarbital phenytoin tiagabine vigabatrin	
Absence seizures	Ethosuximide	sodium valproate (except in women and girls able to have children)	lamotrigine or levetiracetam (as a third-line monotherapy or add-on treatment options)			carbamazepine gabapentin oxcarbazepine phenobarbital phenytoin pregabalin tiagabine vigabatrin

Absence seizures with other seizure types	sodium valproate (except in women and girls able to have children) lamotrigine levetiracetam	lamotrigine or levetiracetam (as a second-line monotherapy or add-on treatment options) **or** ethosuximide (as a second-line add-on treatment)				carbamazepine gabapentin oxcarbazepine phenobarbital phenytoin pregabalin tiagabine vigabatrin
Myoclonic seizures	sodium valproate (except in women and girls able to have children) levetiracetam	levetiracetam (as a second-line monotherapy or add-on treatment)	brivaracetam clobazam clonazepam lamotrigine phenobarbital piracetam topiramate zonisamide			carbamazepine gabapentin oxcarbazepine phenytoin pregabalin tiagabine vigabatrin.
Tonic or atonic seizures	sodium valproate (except in women and girls able to have children) lamotrigine	lamotrigine (as a second-line monotherapy or add-on treatment)	clobazam rufinamide topiramate (consider one of them as a monotherapy or add-on treatment)			carbamazepine gabapentin oxcarbazepine pregabalin tiagabine vigabatrin

Appendix 6. NICE 2022 treatment guidelines for treating some childhood-onset epilepsy syndromes.

Epilepsy syndrome	First-line treatment	Second-line treatment	Third-line treatment	Further treatment options	May exacerbate seizures
Dravet syndrome	sodium valproate monotherapy	sodium valproate and stiripentol and clobazam (as triple therapy)	cannabidiol in combination with clobazam (if the child is over 2 years)	ketogenic diet levetiracetam topiramate.	carbamazepine gabapentin lacosamide lamotrigine oxcarbazepine phenobarbital pregabalin tiagabine vigabatrin
Lennox–Gastaut syndrome	sodium valproate monotherapy	lamotrigine (as a second-line monotherapy or add-on treatment)	cannabidiol in combination with clobazam (if the child is over 2 years) clobazam rufinamide topiramate.	ketogenic diet felbamate (as an add-on treatment)	carbamazepine gabapentin lacosamide lamotrigine oxcarbazepine phenobarbital pregabalin tiagabine vigabatrin
Infantile spasms syndrome	combination therapy with high-dose oral prednisolone and vigabatrin *Consider vigabatrin alone as first-line treatment for infantile spasms in children at high risk of steroid-related side effects, or for infantile spasms	ketogenic diet levetiracetam nitrazepam sodium valproate topiramate			

	that are due to tuberous sclerosis)				
Self-limited epilepsy with centrotemporal spikes	lamotrigine or levetiracetam	carbamazepine oxcarbazepine zonisamide (as second-line monotherapy)	sulthiame (as monotherapy or add-on treatment)		carbamazepine, oxcarbazepine and lamotrigine may rarely exacerbate seizures or the development of another epilepsy syndrome, or affect cognitive performance.
Epilepsy with myoclonic-atonic seizures (Doose syndrome)	levetiracetam or sodium valproate as first-line treatments	ketogenic diet as a second-line monotherapy or add-on treatment	clobazam ethosuximide topiramate zonisamide. (as third-line monotherapy or add-on treatment)		carbamazepine gabapentin oxcarbazepine phenytoin pregabalin vigabatrin

Appendix 7. Article: Early predictors of remission in children and adolescents with new-onset epilepsy: A prospective study

Seizure: European Journal of Epilepsy 110 (2023) 69–77

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Early predictors of remission in children and adolescents with new-onset epilepsy: A prospective study

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ARTICLE INFO

Keywords:
Children and adolescents
New onset seizures
Remission
Epileptogenic lesion
Intellectual and developmental delay
Number of pretreatment seizures

ABSTRACT

Purpose: This study aims to identify predictive factors of a two-year remission (2YR) in a cohort of children and adolescents with new-onset seizures based on baseline clinical characteristics, initial EEG and brain MRI findings.
Methods: A prospective cohort of 688 patients with new onset seizures, initiated on treatment with antiseizure medication was evaluated. 2YR was defined as achieving at least two years of seizure freedom during the follow-up period. Multivariable analysis was performed and recursive partition analysis was utilized to develop a decision tree.
Results: The median age at seizure onset was 6.7 years, and the median follow-up was 7.4 years. 548 (79.7%) patients achieved a 2YR during the follow up period. Multivariable analysis found that presence and degree of intellectual and developmental delay (IDD), epileptogenic lesion on brain MRI and a higher number of pretreatment seizures were significantly associated with a lower probability of achieving a 2YR. Recursive partition analysis showed that the absence of IDD was the most important predictor of remission. An epileptogenic lesion was a significant predictor of non-remission only in patients without evidence of IDD, and a high number of pretreatment seizures was a predictive factor in children without IDD and in the absence of an epileptogenic lesion.
Conclusion: Our results indicate that it is possible to identify patients at risk of not achieving a 2YR based on variables obtained at the initial evaluation. This could allow for a timely selection of patients who require close follow-up, consideration for neurosurgical intervention, or investigational treatments trials.

1. Introduction

It is well established that despite the availability of numerous novel antiseizure medications (ASMs), one third of children with new-onset seizures will not achieve seizure remission [1–3]. These children endure the physical, psychological and social consequences of intractable seizures and face an elevated risk of death [4,5]. Despite its clinical importance, the early prediction of treatment outcome remains a major challenge [6], with only a limited number of large, community-based, long-term studies evaluating early predictors of medical refractoriness in childhood epilepsy [7–9]. Certain childhood electroclinical syndromes, such as the self-limited focal epilepsy with centrotemporal spikes (SeLECTS) are known to have an excellent prognosis, while others, such as the Lennox-Gastaut syndrome, are associated with a

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https://doi.org/10.1016/j.seizure.2023.06.007
Received 22 March 2023; Received in revised form 6 June 2023; Accepted 8 June 2023
Available online 10 June 2023

much poorer outlook [10,11]. Although the determination of a specific electroclinical syndrome could provide guidance on management and clarify long-term prospects, syndromic diagnosis is frequently difficult to ascertain at the time of seizure onset [11]. An alternative approach is to develop a model that can predict treatment outcome based on variables obtained near the time of the initial evaluation. This would enable earlier consideration of surgical intervention or alternative non-medicinal treatments for children at high risk of not achieving seizure remission while avoiding the burden of ineffective polytherapy trials [12].

This prospective study aims to identify the prognostic variables for a two-year remission (2YR) following initiation of treatment with an ASM in children and adolescents with new-onset seizures, solely based on the clinical characteristics, EEG and brain MRI findings obtained at the time of the initial visit. A secondary objective is to calculate remission rates when stratified according to the latest International League Against Epilepsy (ILAE) classification of the epilepsies [11,13].

2. Materials and methods

2.1. Study design

A cohort of children and adolescents with new-onset seizures was identified from an ongoing centralized prospective study conducted at the American University of Beirut Medical Center (AUBMC) in association with the Lebanese Chapter of the International League against Epilepsy (ILAE). Although an official census is not available, it is estimated that the Lebanese population consists of 5.3 million individuals residing in the six governorates [14], with approximately 31% of the population being 17 years of age or younger [15]. This research study is a multicenter collaborative effort involving numerous neurologists distributed across the six governorates. These neurologists refer their patients with newly diagnosed seizures to the AUBMC, where a full clinical evaluation and extensive workup are performed.

As per protocol, the work-up included a detailed history and a thorough description of the events obtained from the patient and an eyewitness, complete physical and neurological examinations, a 3-hour sleep deprived video-EEG recording interpreted by experienced epileptologists, along with an epilepsy protocol brain MRI interpreted by a neuroradiologist with vast experience in the neuroimaging of patients with epilepsy. Patients were subsequently evaluated by telephone consultations and yearly follow-up visits with repeat EEGs as clinically indicated. More frequent follow-up visits were scheduled in case of seizure recurrence or adverse events related to ASM. At each follow-up visit or phone call, information about seizure frequency, changes in drug therapy or posology, adverse events and adherence to treatment were systematically recorded. Adherence to treatment was monitored through inquiries made to the caregiver/patient regarding the administration of ASM as prescribed. For children receiving valproate, carbamazepine, phenytoin or phenobarbital, routine monitoring of serum levels for these medications was conducted. However, due to the unavailability of local facilities for checking serum levels of newer ASMs and the high associated costs involved, which were not affordable for most patients or their parents, the serum levels of these drugs were rarely monitored.

2.2. Inclusion/exclusion criteria

For this study, we enrolled consecutive children ranging from 6 months to 18 years of age who presented with one or more unprovoked seizure between March 2010 and May 2016, and who were initiated on treatment with an ASM at the time of recruitment and had a follow-up of at least two years. Patients who presented with acute symptomatic or febrile seizures, as well as those with a history of functional seizures, alcohol or drug abuse, were excluded. Additionally, children with a follow-up period of less than two years while on ASM treatment and those non-compliant to their prescribed treatment regimen, were excluded. Patients who died or underwent surgery after enrollment were censored at the time of death or surgery.

2.3. Ethical approval and patient consent

This study was approved by the Institutional Review Board of the AUBMC, and all patients enrolled in this study had an informed consent signed by one of their parents.

2.4. Brain MRI and classification of neuro-imaging findings

Brain MRIs were obtained from a 1.5 or 3T scanner (Ingenia; Phillips Healthcare) using an imaging-acquisition protocol that included 3D T1 (1 mm slice thickness) and 3D fast fluid-attenuated inversion recovery (FLAIR; 0.9- or 1-mm slice thickness) of the whole brain with multiplanar reconstruction, axial and coronal inversion recovery (2 mm slice thickness), axial T2 TSE and T2 FFE (4 mm slide thickness) and axial diffusion weighted images (4–5 mm slice thickness). The 3D images were obtained with no interslice gap.

MRI findings were classified as epileptogenic or non-epileptogenic based on previously published criteria [16–18]. MRI abnormalities consisting of isolated subcortical lesions or abnormal signal, nonspecific white matter hyperintensities, hydrocephalus, and brain atrophy were considered incidental findings.

2.5. Sleep deprived electroencephalogram (EEG) and classification of EEG findings

The EEGs were recorded on digital Nicolet machines (Natus^{R} Neurodiagnostics) with electrodes placed according to the International 10–20 system. At the initial visit, a 3-hour sleep deprived video-EEG with sleep recording was recorded from all patients. At each follow-up visit, a 60-minute sleep deprived EEG recording was performed. The EEG obtained at the initial visit were stratified according to the presence or absence of interictal epileptiform discharges (IEDs). Focal IEDs were classified based on their topography, morphology and presence or absence of focal slowing into focal maturational or focal non-maturational discharges [19]. The generalized spike wave discharges (GSWD) of the type seen in patients with a genetic generalized epilepsy (frequency of more than 2.5 Hz associated with a normal background) were labeled as idiopathic generalized discharges [19]. The GSWD of the type seen in patients with a developmental and epileptic encephalopathy (frequency of less than 2.5 Hz associated with a slow and disorganized background with or without concomitant focal or multifocal IEDs) were labelled as symptomatic generalized discharges.

2.6. Assessment of intellectual and developmental delay

All patients underwent an assessment to evaluate for the presence and severity of intellectual and developmental delay (IDD). Children younger than 6 years of age were evaluated using the Denver Development Screening Test [20]. Older children were assessed according to the Diagnostic and Statistical Manual of Mental Disorders criteria, which classifies intellectual delay as mild, moderate, severe, or profound based on deficits in intellectual functioning as well as difficulties in conceptual, social, and practical areas of living [21]. For example, children with mild intellectual delay may struggle with learning abilities and exhibit immaturity in social interactions, with communication and language skills that are more concrete than expected for their age. Children with moderate intellectual delay display marked limitations compared to their peers, with significant differences in social and communicative behavior. However, children with mild and moderate intellectual delay can still care for their personal needs, including eating, dressing and hygiene. Children with severe and profound intellectual delay have limited or very limited language development and have

substantial limitations in the conceptual domains. They require support or are completely dependent on others for all activities of daily living [21]. For the purpose of our analysis, we combined children with severe and profound delays into a single category, and included three groups of IDD (mild, moderate, or severe). To ensure the accuracy and consistency of the assessments, research fellows with specialized training in administering these tests were responsible for conducting the evaluation and scoring the degree of deficit. These chosen assessment tools were selected based on factors such as feasibility in terms of cost, accessibility, time requirements, and training considerations. Since our aim was to identify predictors of seizure remission based on baseline clinical variables, the IDD severity score determined during the initial visit was used for the analyses.

2.7. Seizure types and determination of the electroclinical syndrome

Seizure types were classified according to the latest ILAE 2017 classification of seizure types [22]. To ensure that the correct diagnosis of the epilepsy syndrome was made, the case report file of each child was entirely reviewed. The electroclinical syndromes were classified according to the latest International League Against Epilepsy (ILAE) classification of the epilepsies [11,13] with children stratified into one of five categories: [1] self-limited focal epilepsy, [2] genetic generalized epilepsy, [3] non-structural focal epilepsy, [4] structural focal epilepsy, [5] developmental and epileptic encephalopathy.

2.8. Outcome

A 2YR was defined as achieving at least two consecutive years of complete seizure freedom at any time during the entire follow-up period. Time to initial 2YR was defined as the elapsed time between treatment initiation and the time when a two-year seizure freedom was attained.

2.9. Variables

The following variables were collected for each patient at the time of enrollment in the study: [1] demographics; [2] disease characteristics (age at seizure onset, seizure types at onset, number of seizure types at onset, pretreatment number of seizures, time of seizure occurrence); [3] epilepsy risk factors (number of risk factors, family history of epilepsy, parental consanguinity, perinatal insult, febrile seizures, head trauma, CNS infection); [4] IDD (presence and severity); [5] IED types on initial EEG; [6] Brain MRI results (presence or absence of epileptogenic lesion).

2.10. Statistical analysis

Descriptive results were reported for the demographic and clinical characteristics. The cumulative time-dependent probability of 2YR was calculated using Kaplan-Meier survival tables and curves. Cox proportional hazards model was used to identify variables associated with 2YR. Assumptions of proportional hazards was tested using Log-Log. Variables yielding p-values < 0.2 in univariable analysis were tested in a multivariable analysis with significance level set at 0.05. Data were presented as hazard ratios (HR) and adjusted HR with 95% confidence intervals (CI).

In addition, a recursive partition analysis was performed to identify variables associated with higher or lower probabilities of achieving a 2YR. For this analysis, we used the Chi-square Automatic Interaction Detector with cross-validation. At each step, the Chi-square Automatic Interaction Detector algorithm chooses the independent variable that has the strongest interaction with the dependent variable using P values with a Bonferroni correction as splitting criteria. The final result is a decision tree with various nodes that can be used to predict the probability of achieving a 2YR in each subgroup. Statistical significance was set at the 5% level. All statistical analyses were performed using SPSS, version 23.

3. Results

Of the 827 enrolled children, 139 were excluded for the following reasons: 72 were lost to follow-up or had a follow-up of less than two years and 67 were poorly compliant or received ASM for less than two years. This left 688 children who met the inclusion/exclusion criteria and who were included in the analyses (Fig. 1). The distribution of patients included in this study closely mirrored the geographical distribution of the population across Lebanon's six administrative governorates. Specifically, within our study cohort, 16% of the children resided in the Beirut governorate, 32% in Mount Lebanon, 23% in North Lebanon, 13% in the Bekaa, and 16% in South Lebanon and Nabatieh.

3.1. Demographic characteristics and epilepsy risk factors

The demographic characteristics and epilepsy risk factors of the study population are summarized in Table 1a. More than half of the children were males (59.2%) and 181 (26.3%) had IDD. The median age at time of seizure onset was 6.7 years (interquartile range (IQR) 2.3–11.0 years). The children were followed up for a mean duration of 7.2 years (range: 2.0–11.6 years; standard deviation: 2.3 years) and a median of 7.4 years (IQR 5.9–9.0 years). Risk factors for epilepsy were present in 459 children (66.7%) and included 208 children (30.2%) with a family history of epilepsy, 109 children (15.8%) born from consanguineous marriage, and 112 children (16.3%) with a history of perinatal insult.

3.2. Clinical characteristics

The clinical characteristics of the study population are summarized in Table 1b. The majority of patients (77.8%) experienced a single seizure type at the time of their initial evaluation. The most common seizure type was focal impaired awareness seizures (FIAS) which occurred in 267 children (38.8%). This was followed by focal to bilateral tonic-clonic seizures (FBTC) in 138 children (20.1%), focal aware seizures in 83 children (12.1%) and generalized onset tonic-clonic seizures (GOTC) in 72 children (10.5%). Prior to treatment initiation, 350 children (50.9%) experienced between one and five seizures, while 233 children (33.9%) experienced more than 100 seizures. This typically was the case in children who experienced frequent daily absence seizures ($n = 82$), myoclonic seizures ($n = 55$), or epileptic spasms ($n = 67$). A small percentage (19.2%) experienced both nocturnal and diurnal seizures. IEDs were observed on the initial EEG of 487 children (70.8%). GSWD of the idiopathic type and focal non-maturational discharges occurred more frequently (23.8% and 24.0% respectively) than GSWD of the symptomatic type and focal maturational discharges (12.4% and 12.1% respectively). An epileptogenic lesion was present on the brain MRI of 191 (27.8%) children, with MCD identified in 61 (31.9%) and hypoxic injury in 46 (24.1%). Out of the 191 patients with epileptogenic lesions detected on brain MRI, 140 exhibited epileptiform discharges that lateralized to the side of the lesions. Among the remaining 51 patients, 35 displayed no interictal discharges on EEG, and 16 patients exhibited discordant or multifocal epileptiform discharges. In cases where no associated epileptiform discharges were present, the brain lesion was considered likely epileptogenic, as the seizure semiology was concordant with the location of the brain lesion. Of the 10 patients with discordant epileptiform discharges, 6 showed hypsarrhythmia on their EEG recordings.

3.3. Treatment characteristics

During the follow-up period, 322 children (46.8%) were prescribed only one ASM, while 187 children (27.2%) received two ASMs, either as monotherapy or in combination. The number of ASMs prescribed ranged from 1 to 10 with a median of two drugs. The patients were treated with

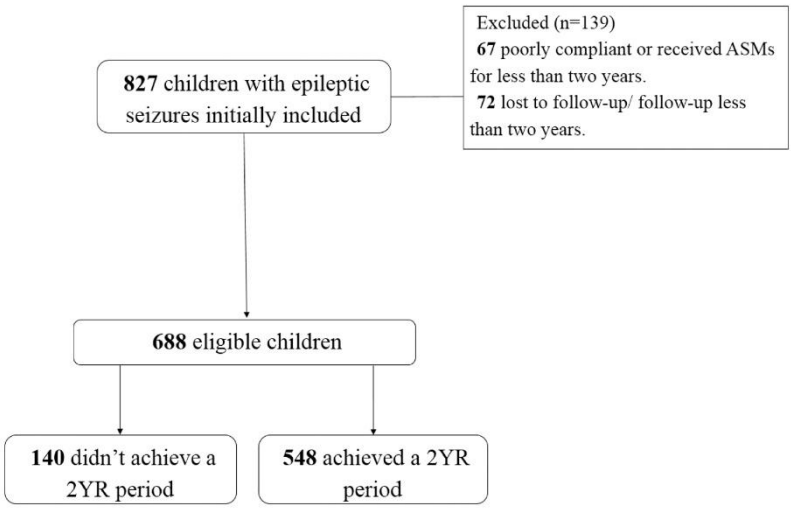

Fig. 1. Flow chart of the study cohort. 2YR: 2-year remission, ASMs: antiseizure medications.

Table 1a
Demographic characteristics and epilepsy risk factors of the study population.

Variable	Mean (STD)	Range	Median (IQR)
Age at seizure onset (years)	7.0 ± 5.0	0.5–17.6	6.7 (2.3–11.0)
Duration of follow-up (years)	7.2 ± 2.3	2.0–11.6	7.4 (5.9–9.0)
Variable	**N (%)**		
Gender			
Male	407 (59.2)		
Female	281 (40.8)		
Age at seizure onset			
0.5 <2 yrs	157 (22.8)		
2-<5 yrs	116 (16.9)		
5-<12 yrs	272 (39.5)		
12-<18 yrs	143 (20.8)		
Intellectual and developmental delay			
None	507 (73.7)		
Mild	58 (8.4)		
Moderate	52 (7.6)		
Severe	71 (10.3)		
Presence of epilepsy risk factors			
Yes	459 (66.7)		
Number of epilepsy risk factors			
None	229 (33.3)		
1	266 (38.7)		
2	159 (23.1)		
≥3	34 (4.9)		
Type of epilepsy risk factor			
Family history of epilepsy	208 (30.2)		
Consanguinity	109 (15.8)		
Perinatal insult	112 (16.3)		
Febrile seizures	85 (12.4)		
Head trauma	36 (5.2)		
CNS infection	15 (2.2)		

STD: standard deviation; IQR: interquartile range; CNS: central nervous system.

an ASM for a mean duration of 4.0 ± 1.8 years (range: 2.0–10.5 years). The most frequently prescribed ASM was valproate (73.4%), followed by levetiracetam (32.1%). Nonpharmacological treatments were received by 51 children (7.4%), that included 23 who underwent epilepsy surgery, 29 inserted with a vagus nerve stimulator, and two treated with the ketogenic diet.

3.4. Remission rates

To date, 548 children (79.7%) have achieved a 2YR. The median time to achieve a 2YR was 2.1 years (95% CI: 2.0–2.1), with a range of 2.0 to 9.7 years. The cumulative probabilities of achieving a 2YR were 43.1% (95% CI: 39.4–46.8%) at 24 months, 69.3% (95% CI: 65.9–72.9%) at 36 months, 75.5% (95% CI: 72.1–78.8%) at 48 months, 81.7% (95% CI: 78.6–84.8%) at 72 months, and 86.6% (95% CI: 83.3–90.0%) at 120 months after treatment initiation (Fig. 2). At last follow-up, 502 (73.0%) of the 688 children included in our study experienced a terminal two-year remission.

3.5. Determinants of remission

3.5.1. Univariable analysis

Univariable analysis showed that several factors were associated with a lower probability of remission. These included a younger age at seizure onset, a greater number of pretreatment seizures, experiencing three or more types of seizures at onset, the presence and degree of IDD, the presence of an epileptogenic lesion on MRI, mixed time of seizure occurrence (both nocturnal and diurnal), a history of perinatal insult, parental consanguinity, and the presence of focal non-maturational or generalized discharges of the symptomatic type (Table 2).

3.5.2. Multivariable analysis

In multivariable analysis (Table 2), factors that independently predicted a lower probability of remission were a greater number of seizures prior to treatment initiation, the presence and severity of IDD and the presence of an epileptogenic lesion on MRI.

Children who experienced more than 100 seizures prior to treatment initiation with an ASM had a lower probability of achieving a 2YR compared to those who experienced up to five seizures (HR= 0.7, 95% CI: 0.5–0.9, $p = 0.011$). This probability was further reduced for children with a history of 11–100 seizures prior to treatment (HR= 0.6, 95% CI 0.4–0.8, $p = 0.002$). The probability of achieving a 2YR varied depending on the presence and severity of IDD. While no significant difference was found between children with mild or moderate IDD and those with no IDD, the probability of achieving a 2YR was significantly lower in children with severe IDD (HR= 0.4, 95% CI 0.2–0.6, $p< 0.001$) (Supplementary Figure 1). Finally, the presence of an epileptogenic lesion on brain MRI significantly reduced the probability of achieving a

Table 1b
Clinical characteristics of the study population.

Seizure types at presentation [a]	
Focal onset	
Focal impaired awareness seizures	267 (38.8)
Focal aware seizures	83 (12.1)
Focal to bilateral tonic-clonic seizures	138 (20.1)
Generalized onset seizures	
Generalized onset tonic-clonic seizures [b]	72 (10.5)
Absence seizures	82 (11.9)
Myoclonic jerks	55 (8.0)
Epileptic Spasms	67 (9.7)
Other[c]	32 (4.7)
Unknown onset	
Unknown-onset tonic-clonic seizures	69 (10.0)
Pretreatment number of seizures	
1–5	350 (50.9)
6–10	42 (6.1)
11–100	63 (9.2)
>100	233 (33.9)
Number of seizure types at presentation	
1	535 (77.8)
2	127 (18.5)
≥3	26 (3.8)
Time of seizure occurrence	
Nocturnal	162 (23.5)
Diurnal	394 (57.3)
Mixed	132 (19.2)
IED on EEG	
No	201 (29.2)
Yes	487 (70.8)
IED type on EEG	
Focal	
Maturational	83 (12.1)
Non-maturational[d]	165 (24.0)
Generalized	
Idiopathic[d]	164 (23.8)
Symptomatic	85 (12.4)
Epileptogenic lesion on MRI[*]	
Yes	191 (27.8)
No	489 (71.1)
Type of Epileptogenic lesion	
Malformations of cortical development	61 (31.9)
Periventricular leukamalacia/hypoxia	46 (24.1)
Vascular	31 (16.2)
Mesial temporal sclerosis	15 (7.9)
Neurocutaneous syndromes	13 (6.8)
Other[e]	25 (13.1)

IED: interictal epileptiform discharges; EEG: electroencephalogram; MRI: magnetic resonance imaging.

[a] Total percentage above 100% because some children experienced more than one seizure type at presentation.

[b] Generalized tonic-clonic seizures were considered of generalized onset if the child had definite absence seizures or myoclonus, or if the event was witnessed from onset with no signs of focality.

[c] Other seizure types include tonic seizures in 13 children (1.9%), eyelid myoclonia in 9 children (1.3%), drop attacks in 8 children (1.2%) and myoclonic absence and myoclonic-atonic seizures in one child each (0.1%).

[d] 10 children were diagnosed with photosensitive occipital lobe epilepsy and had both focal and idiopathic generalized epileptiform discharges.

[*] A brain MRI was not performed on 8 children.

[e] Other lesions consisted of post-infectious encephalomalacia with cortical gliosis in 7 (3.7%), metabolic disorders and post-traumatic encephalomalacia and gliosis in 5 children each (2.6%), tumors in 5 children (2.2%) and leukodystrophy in 3 (1.5%).

2YR (HR=0.6, 95% CI 0.5–0.8, $p< 0.001$) (Supplementary Figure 2).

3.5.3. Recursive partition analysis

The recursive analysis identified those same variables that partitioned the patients into a decision tree with five groups (Fig. 3). The first important predictor of failure to achieve remission was the presence and severity of IDD, which classified children into three groups: those with no IDD, those with mild or moderate IDD and those with severe IDD. 60% of children with severe IDD and 31.5% of children with mild or moderate IDD failed to achieve a 2YR compared to 10.6% of children with no IDD.

The next predictor variable, the presence or absence of an epileptogenic lesion on brain MRI, only applied to children with no IDD where 29.1% of children with a lesion failed to achieve a 2YR compared to 7.1% of children with no lesion. Finally, the terminal predictor in children with no IDD and no epileptogenic lesion was the number of seizures prior to treatment initiation; 13.7% of children with more than 10 seizures prior to treatment initiation failed to achieve remission, compared to 3.4% in children with a lower number of seizures.

3.6. Remission rates stratified according to epilepsy syndromes

The majority of children in the study were diagnosed with focal epilepsy, with 121 children (17.6%) diagnosed with a self-limited focal epilepsy (SeLFE), 132 (19.2%) with a structural focal epilepsy and 186 (27.0%) with a non-structural focal epilepsy. 155 (22.5%) children were diagnosed with a genetic generalized epilepsy (GGE), while 94 (13.7%) were diagnosed with a developmental and epileptic encephalopathy (DEE). The associated 2YR rates for each syndrome are shown in Fig. 4. The groups of children most likely to achieve a 2YR were those diagnosed with a SeLFE (97.5%), GGE (92.9%) and non-structural focal epilepsies (87.1%). In contrast, there was a lower likelihood of achieving a 2YR in children diagnosed with a structural focal epilepsy (59.8%) or DEE (47.9%). It is worth noting the variable distribution of epilepsy syndromes across different age groups. The highest prevalence of DEE was observed in children with seizure onset between 0 and 2 years (44.6%), while the lowest between 12 and 18 years (0.7%). Conversely, the lowest prevalence of GGE was in children with seizure onset between 0 and 2 years (4.5%), while the highest was in children with onset between 12 and 18 years (42.0%) (Supplementary Figure 3).

4. Discussion

Our results indicate that 79.7% of children with new-onset seizures will achieve a 2YR after treatment initiation. The independent negative predictors of a 2YR include the presence and severity of IDD, the presence of an epileptogenic lesion on brain MRI and the number of pretreatment seizures. These results suggest that it is possible to identify children who are at risk of not achieving a 2YR based on variables obtained at the time of initial evaluation.

The percentage of children who achieved a 2YR in our study is comparable to the 74% rate reported in a previous study of 594 children with newly diagnosed epilepsy [23]. The slightly lower remission rate in the previous study is likely due to a shorter follow-up period (median of 5.3 years compared to 7.4 years in our study) and a younger age at seizure onset (median of 5.3 years compared to 6.7 years in our study). Both studies, however, are consistent in showing that most children with new-onset seizures will reach a 2YR at some point during their clinical course, with most remissions occurring in the early years following treatment initiation.

Our data ascertaining that the presence and severity of IDD is one of the key factors impacting the likelihood of achieving a 2YR is consistent with the findings of previous studies [24–26]. This is however the first study to clearly indicate that the presence and severity of IDD are the most significant baseline variables that influence the probability of attaining a 2YR. This conclusion was supported by the adjusted hazard ratio and the principal predictor variable of the recursive analysis, which showed that children with normal development had the highest likelihood of achieving a 2YR, those with mild to moderate IDD had a lower probability, and those with severe IDD had the lowest odds.

In this study, 27.8% of children were found to have an epileptogenic lesion on their brain MRI. Previous studies reported etiologically related neuroimaging abnormalities in 13%–18% of children with new-onset seizures [27–29]. The higher percentage in our study is likely due to

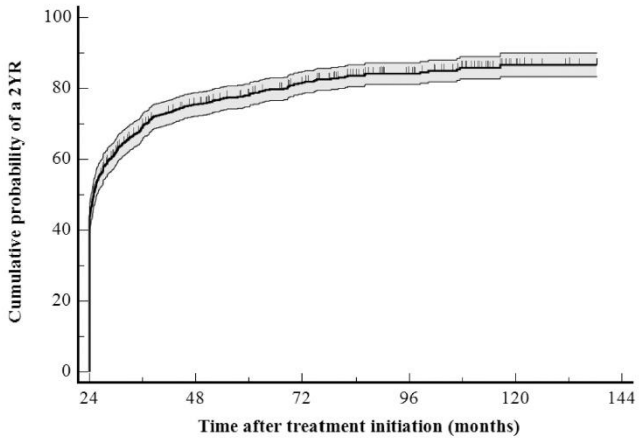

Fig. 2. Kaplan-Meier Curve: Cumulative probability of achieving a two-year remission (2YR) following treatment initiation. Dashed lines represent censored data. Gray shade represents 95% confidence interval.

Table 2
Univariable and multivariable Cox regression results for two-year remission by clinical characteristics, EEG and brain MRI obtained at the initial visit.

	Unadjusted HR			Adjusted HR		
Comparison	HR	95%CI	p-value	HR	95%CI	p-value
Pretreatment number of seizures						
1–5	1		–	1		–
6–10	0.92	0.65–1.29	0.612	0.82	0.57–1.18	0.284
11–100	0.53	0.38–0.74	<0.001	0.58	0.41–0.82	0.002
>100	0.63	0.52–0.77	<0.001	0.70	0.53–0.92	0.011
Intellectual and developmental delay						
None	1		–	1		–
Mild	0.65	0.48–0.89	0.007	0.79	0.56–1.12	0.181
Moderate	0.49	0.34–0.71	<0.001	0.68	0.44–1.03	0.072
Severe	0.25	0.17–0.37	<0.001	0.35	0.21–0.59	<0.001
Presence of epileptogenic lesion on MRI	0.47	0.38–0.58	<0.001	0.64	0.49–0.82	<0.001
Female vs. male	0.98	0.82–1.16	0.769			
Age at seizure onset						
0.5-<2 yrs	1		–	1		–
2-<5 yrs	1.44	1.08–1.91	0.012	0.95	0.69–1.30	0.759
5-<12 yrs	1.7	1.34–2.16	<0.001	1	0.76–1.35	0.903
12-<18 yrs	2.03	1.56–2.65	<0.001	1	0.73–1.38	0.962
Number of seizure types at onset						
1	1		–	1		–
2	0.91	0.73–1.13	0.385	1.01	0.8–1.27	0.986
≥3	0.41	0.23–0.7	0.001	0.56	0.3–1.03	0.062
Time of seizure occurrence						
Nocturnal	1		–			–
Diurnal	1.05	0.86–1.28	0.645	1.16	0.93–1.4	0.188
Mixed	0.67	0.51–0.87	0.003	0.96	0.71–1.31	0.830
Presence of epilepsy risk factors	0.91	0.76–1.08	0.304			
Number of epilepsy risk factors						
None				1		–
1	1		–	1.1	0.87–1.36	0.414
2	0.82	0.66–1.03	0.093	0.99	0.7–1.39	0.950
≥3	0.72	0.47–1.11	0.136	0.99	0.55–1.80	0.991
Perinatal insult	0.67	0.52–0.86	0.002	1.04	0.76–1.43	0.794
Febrile seizure	1.19	0.94–1.52	0.153	1.26	0.93–1.72	0.135
Head trauma	1.15	0.81–1.65	0.434			
CNS infection	0.7	0.37–1.31	0.26			
Parental consanguinity	0.73	0.6–0.9	0.003	0.85	0.64–1.12	0.241
Family history of epilepsy	1.05	0.89–1.24	0.579			
IED type on initial EEG						
No discharges	1		–	1		–
Focal maturational	1.23	0.95–1.61	0.118	1.05	0.78–1.42	0.747
Focal non-maturational	0.69	0.54–0.88	0.002	0.82	0.63–1.06	0.135
Generalized idiopathic	1.19	0.96–1.5	0.12	1.14	0.85–1.53	0.363
Generalized symptomatic	0.37	0.26–0.52	<0.001	1.09	0.66–1.77	0.742

Abbreviations: CI; confidence interval; HR: hazard ratio; CNS: central nervous system; IED: interictal epileptiform discharges; EEG: electroencephalogram; MRI: magnetic resonance imaging.

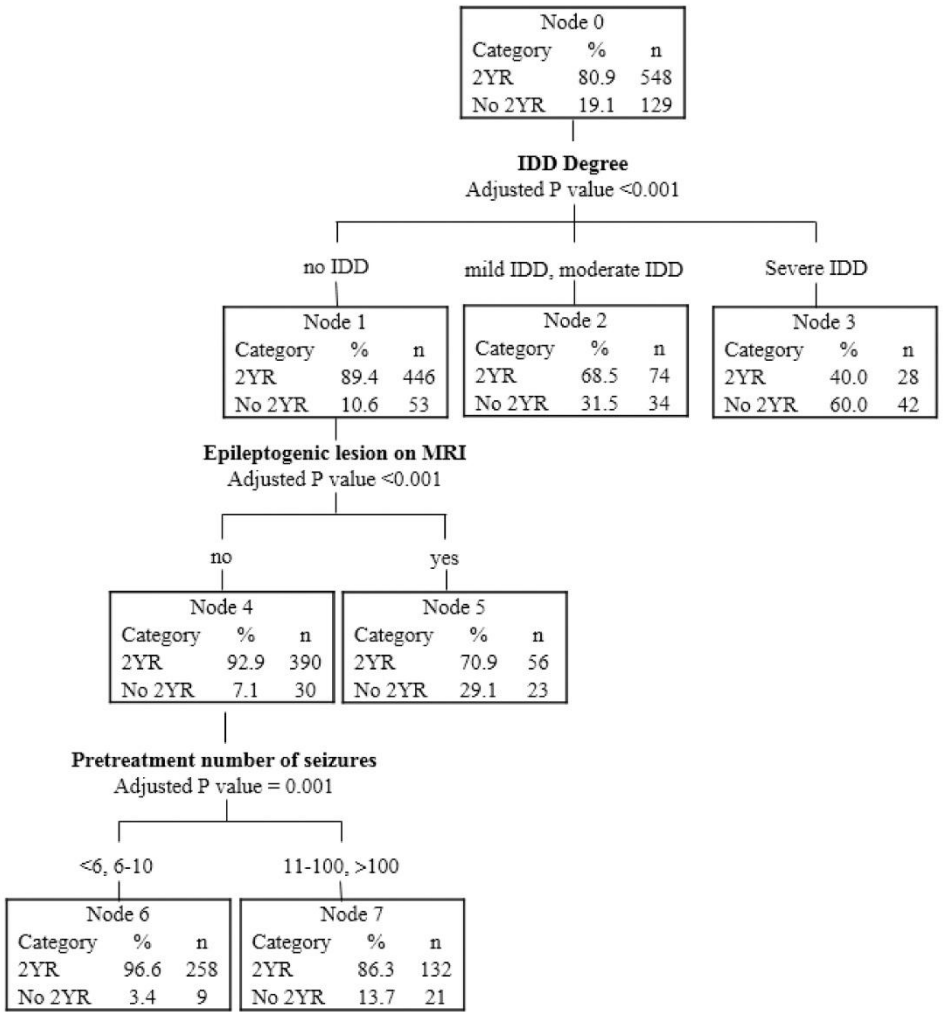

Fig. 3. Recursive partition analysis stratified children into a decision tree with 5 groups based only on the presence and severity of IDD, presence of epileptogenic lesion on MRI, and pretreatment number of seizures. IDD: intellectual and developmental delay, MRI: magnetic resonance imaging, 2YR: two-year remission.

obtaining a dedicated epilepsy protocol MRI on all children, whereas prior studies evaluated children with brain CT and non-epilepsy protocol MRI [27,28,30] or excluded children with IDD [29]. Those results emphasize the importance of obtaining an epilepsy protocol brain MRI as the presence of an epileptogenic lesion was a significant negative predictor for achieving a 2YR. Most studies evaluating the prognosis of childhood epilepsy have reported that a remote symptomatic etiology was predictive of poor seizure outcome [7,8,23,31,32]. However, in our study, the recursive partitioning analysis found that this variable was only significant in children without evidence of IDD, indicating that the presence of IDD supersedes the detection of an epileptogenic lesion as a determinant of achieving a 2 YR. Although the relationship between the nature of the pathologic substrate and medical refractoriness has been studied in adults [33–35], such analysis was beyond the scope of this study and will be the subject of future research.

Our findings are also consistent with other studies [8,9,36–39] that have shown that a higher number of pretreatment seizures is associated with a significantly lower probability of attaining a 2YR. However, the recursive partitioning analysis in our study found that this factor was only significant in children without IDD and without a lesion on brain MRI. Actually, nearly all children in this study with more than 100 seizures prior to treatment initiation experienced absence seizures, myoclonic seizures or epileptic spasms. Additionally, a subgroup analysis in our study revealed that the association between the number of pretreatment seizures and the likelihood of achieving a 2YR was only significant for children with focal-onset seizures. This finding is concordant with other observational studies [40,41], that when critically reviewed [42], documented that the relationship between high initial seizure frequency and poor outcome was only true for children experiencing focal impaired awareness seizures. Our data therefore support the conclusion that the type of epilepsy rather than the number of pretreatment seizures is the major variable that impacts outcome [42].

In our univariable analysis, we found that seizure onset within the

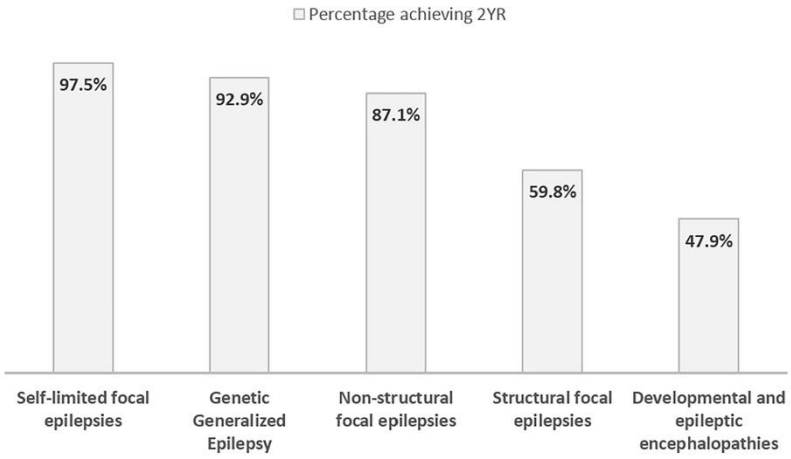

Fig. 4. Percentages of children achieving a two-year remission (2YR) stratified according to the epilepsy syndromes.

first two years of life was associated with a significantly lower probability of achieving a 2YR, a result in line with previous studies [8,43,44]. Nevertheless, in a multivariable analysis, we and others [9] found that there was no independent association between these variables. The divergent outcomes across different age groups are therefore more likely attributable to the prevalence of specific epilepsy syndromes in various age ranges. For instance, in our study, DEE was the most common diagnosis in children with seizure onset in the first two years of life, whereas GGE was the most prevalent among those with onset between 12 and 18 years.

Previous studies that evaluated the prognostic value of IED have yielded conflicting results. While some investigators found no significant association between prognosis and the presence of IED [8,23,26], others indicated that their presence was associated with a poorer outcome [43]. Those studies however only assessed for the presence or absence of any type of IED [8,23,26] or at best categorized them into focal or generalized discharges [43]. In our study, we divided the IED into four types and found that symptomatic generalized discharges and focal non-maturational discharges were associated with a significantly lower likelihood of attaining a 2YR in the univariable analysis. This association was however not significant in the multivariable analysis with the recursive partitioning analysis indicating that the coexistence of IDD in the case of symptomatic generalized discharges and epileptogenic lesions in the case of focal non-maturational discharges overshadowed the importance of those types of IEDs as significant negative predictor variables.

Our study has several strengths that make its findings robust and reliable. Those include its prospective design and the inclusion of a large number of consecutive children referred from all governorates of the country, which enhances the generalizability of the results. Additionally, the study evaluated many variables that might impact prognosis and included a long-term follow-up, which allowed for a comprehensive evaluation of the outcomes. Furthermore, the seizures and epilepsies were classified according to the ILAE guidelines, providing a standardized and reliable classification system. Finally, this study not only confirmed the negative association between certain variables and the probability of a 2YR but is the first to perform a recursive analysis that allowed for a prioritization and splitting of those independent factors. Our study has also several limitations that need to be acknowledged. Firstly, the duration of follow-up was variable, which might have influenced the results. Secondly, infants below the age of 6 months at the time of their initial presentation were not included according to the study protocol. Due to the higher prevalence of drug-resistant epilepsy in this age group, this exclusion might have impacted the results by potentially overestimating the remission rates. Another limitation is that some children were evaluated with a 1.5 Tesla MRI, which might have led to an underestimation of epileptogenic lesions. Furthermore, the serum levels of the newer ASMs were not routinely checked, and we relied on the information provided by caregivers or the parents regarding treatment adherence for these particular ASMs. In addition, in children younger than 6 years of age, we relied on the Denver Development Screening Test to assess for the presence and severity of IDD without confirmation from another assessment tool. Finally, genetic testing was not systematically obtained, especially in children with a DEE, which might have impacted the results. Future studies should aim to validate and expand upon the predictive variables identified in our investigation and to assess their generalizability to diverse populations.

5. Conclusions

This study provides valuable insights into the prognosis of children with new-onset seizures. The results indicate that the likelihood of achieving a 2YR can be assessed at the time of the initial evaluation, providing additional perspectives for counseling patients and their parents. The findings will allow for a timely selection of children who might require close follow-up or early neurosurgical intervention, or for management with investigational treatments.

Funding

This work was supported by the Lebanese National Council for Scientific Research [Grant number: LCR 114110 522214]; and the American University of Beirut [Grant number: 1131613 52480 115372099990000].

Data availability

Data available on request from the corresponding author.

Declaration of Competing Interest

None of the authors has any conflict of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in

the online version, at doi:10.1016/j.seizure.2023.06.007.

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