Drug-resistant epilepsy and its selected complications in children

Padaczka lekooporna oraz jej wybrane powikłania u dzieci

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ABSTRACT

Drug-resistant epilepsy (DRE) in children is one of the most diagnosed disorders of the nervous system. Despite the availability of pharmacotherapy with various mechanisms of action, drug resistance leads to the inability to achieve the intended therapeutic effect. Considering the complex etiology of this disease entity, there is an urgent need to deepen our knowledge regarding the determinants of DRE, as well as the potential for improving the quality of life for patients and their families. This paper provides an overview and description of the latest advancements and current state of knowledge related to the clinical characteristics, epidemiology, possible complications, and especially genetic basis of DRE in the Polish population of children.

KEYWORDS

complications, drug-resistant epilepsy, genetic basis

STRESZCZENIE

Padaczka lekooporna (*drug-resistant epilepsy* – DRE) u dzieci jest jedną z najczęściej diagnozowanych chorób układu nerwowego. Pomimo dostępności farmakoterapii o różnych mechanizmach działania lekooporność determinuje brak możliwości osiągnięcia zamierzonego efektu terapeutycznego. Mając na uwadze złożoną etiologię omawianej jednost-ki chorobowej, istnieje pilna potrzeba zgłębiania wiedzy w zakresie determinantów DRE, jak i możliwości poprawy jakości życia pacjentów oraz ich rodzin. Praca stanowi opis z podsumowaniem najnowszych osiągnięć i aktualnego stanu wiedzy odnoszącego się do charakterystyki klinicznej, epidemiologii, możliwych powikłań, a szczególnie podło-ża genetycznego DRE w polskiej populacji dzieci.

SŁOWA KLUCZOWE

powikłania, padaczka lekooporna, podłoże genetyczne

Introduction

Epilepsy is one of the most commonly observed neurological disorders in children. As reported by the World Health Organization (WHO), epilepsy affects approximately 50 million people worldwide [1]. In the United States alone, around 3 million adults and nearly 500,000 children suffer from this medical condition [2], with about one-third of patients exhibiting drug resistance [3], which means the incidence of drug-resistant epilepsy (DRE) was 0.7––1.36 per 1000 inhabitants in Europe [4,5] and 0.7––0.8 per 1000 inhabitants in other countries of the world [6,7].

Epilepsy constitutes a group of disorders with diverse etiologies and variable courses, which determines the challenges in its diagnosis [8]. Despite the medical advancements in recent years and the deepening of knowledge in this field, epilepsy continues to pose a challenge for both medical professionals and researchers [9].

Patients diagnosed with epilepsy may simultaneously exhibit resistance to treatment, which is a criterion for the diagnosis of DRE [10]. In the pathomechanism of drug resistance, processes with neuroinflammatory, autoimmune, and neurodegenerative characteristics play a significant role [11]. Recently, the significance of dysbiosis has also been considered in this context [12]. The treatment of DRE is a complex and prolonged process. It requires an individualized approach to the patient, exposing children to potential side effects such as decreased concentration, hyperactivity, drowsiness, as well as pain and headaches [8,9]. Epilepsy significantly diminishes the quality of life for patients and increases the risk of comorbidities such as intellectual disability or depression, and the sequential use of medications or long-term combination therapies contribute to liver damage [10,13,14]. Patients are at risk of premature death, with their life expectancy shortened by approximately 2–10 years. Epilepsy also limits children socially, often forcing them to abandon their passions or subjecting them to stigma from peers [9]. It is important to note that the discussed medical condition disrupts the proper functioning not only of the child but also of their entire family.

Therefore, a precise understanding of the factors contributing to the emergence of drug resistance becomes crucial. This will allow the appropriate selection of pharmacotherapy, minimizing the negative effects of treatment, and ultimately improving the quality of life for pediatric patients and their families [15].

Clinical characteristics of pediatric DRE

Definitions of DRE

The Internatioal League Against Epilepsy (ILAE) has proposed that epilepsy should be considered drug--resistant if, despite the appropriate use of two properly chosen, administered, and tolerated antiepileptic drugs in combination or monotherapy, seizure remission has not been achieved [15]. This definition from 2010 is used in Poland [16]. On the other hand, according to Camfield's proposition from 1996, epilepsy is deemed drug--resistant when at least one seizure occurs within a 2-month period of treatment during the first five years of therapy. If the therapy continues beyond this period, epilepsy can be considered drug-resistant if at least one seizure occurs within a year [17]. Thus, DRE is a concept that currently lacks a clear and unequivocal definition [18].

Epidemiology along with predisposing factors for the occurrence of DRE

Epidemiological studies of epilepsy employ two parameters: the incidence rate and the prevalence rate [19].

The inconsistencies in defining DRE contribute to challenges in obtaining in-depth estimates regarding its occurrence and prevalence. An analysis of 35 studies on DRE published between 1980 and 2015 revealed an incidence rate of around 30% and a prevalence rate of 15% [20].

Despite the availability of numerous antiepileptic drugs, the proportion of individuals with DRE remains comparable to that of the 1960s [21].

A pivotal component of epidemiological research is to identify factors predisposing to drug resistance. Among the most commonly mentioned factors are the age at onset, gender, duration and etiology of epilepsy, initial seizure type, presence of febrile or neonatal (febrile) seizures in the patient's history, family history of epilepsy, presence of neurological deficits, the frequency of seizures prior to treatment initiation, as well as electroencephalography (EEG) and neuro-imaging findings [19]. An analysis aimed at identifying the predictors of DRE revealed that one of the major risk factors is the occurrence of epilepsy within the first year of life. A relationship between drug resistance and psychomotor delay as well as intellectual impairment has also been observed. Language, attention, and behavior disorders also play a significant role. Furthermore, a key indicator of drug

resistance can be the frequency of seizures prior to the initiation of therapy.

It is important to note that due to the multifactorial nature of DRE, the manifestation of the phenotype depends not only on the individual effects of specific risk factors but also on their mutual interactions. Considering these dependencies is crucial in estimating the risk of DRE, as well as in selecting appropriate treatment and providing adequate medical care.

Pathogenesis of DRE

Based on the available literature, several hypotheses have been proposed regarding the mechanisms that could contribute to the development of resistance to antiepileptic drugs [22]. Below is a brief summary of the most important two:

The first main one is the pharmacokinetic hypothesis. It suggests that the overexpression of transporters responsible for drug elimination from internal organs leads to decreased concentrations of antiepileptic drugs in the bloodstream, resulting in insufficient drug levels crossing the blood-brain barrier to achieve the desired therapeutic effect at the seizure focus [23]. The second main one is the pharmacodynamic hypothesis. This hypothesis assumes that interactions between individual drugs may result in therapeutic synergism or antagonism [24]. Other hypotheses are derivatives of those mentioned above.

The neuronal network hypothesis suggests that epileptic seizures, by causing changes in brain plasticity, may lead to the formation of improperly functioning neuronal networks that prevent the penetration of antiepileptic drugs into the seizure focus. However, a weakness of this assumption is that this pathomechanism does not lead to drug resistance in all patients [22,25].

The internal intensity hypothesis states that interactions between neurobiological factors contribute to both drug resistance and the intensity of epilepsy. Frequent seizures before starting pharmacotherapy are associated with a more intense disease phenotype, thereby predisposing to drug resistance [26].

Another hypothesis, the genetic variant hypothesis, points to genetic variability as a primary cause of drug resistance in epilepsy [10]. An individual's response to antiepileptic drugs may result from mutations in genes encoding drug transporters, metabolizing the enzymes for these drugs, and genes encoding ion channel subunits [27].

The target site hypothesis is based on the assumption that changes in the properties of drug target sites can lead to reduced organism sensitivity to the drugs themselves [28]. Nevertheless, current clinical evidence mainly relates to sodium channel insensitivity to carbamazepine [10].

The transporter hypothesis suggests that drug resistance is caused by the excessive expression of multidrug transporters in the blood-brain barrier, thereby limiting drug access to the brain [29]. In this context, attention is drawn to P-glycoprotein, which is excessively expressed in the brain structures of patients with DRE [30].

Conversely, the epigenetic hypothesis posits that epileptic seizures may result in excessive depolarization of neuronal membranes and mediate epigenetic modifications involving genome methylation, histone modifications, chromatin remodeling, post-translational modifications, and non-coding RNA-based changes [31,32].

It should be noted that the conducted studies have not provided definitive evidence confirming the validity of any specific hypothesis mentioned above.

Genetic basis in manifestation of DRE in children and/or epileptic syndromes associated with drug resistance

Epileptic syndromes exhibit significant genetic heterogeneity. It should be noted that the phenotype of DRE may manifest within specific medical conditions or neurodevelopmental disorders with distinct genetic backgrounds.

The following table includes genetic factors that could contribute to the manifestation of epilepsy/epileptic syndromes. Mutations or polymorphic variants in these genes may potentially predispose to the occurrence of drug resistance phenomenon (Table I).

Table I. Genes associated with epilepsy and/or drug-resistant seizure syndromes (based on [33])

Phenotype	Genes
Early infantile epileptic encephalopathy (EIEE)	GABRA1, GABRB3, KCNQ2, KCNT1, SCN2A, SCN8A, AARS, DOCK7, GUF1, SLC12A5, TBC1D24
Dravet syndrome	SCN1A, SCN9A
Myoclonic-atonic epilepsy (MAE)	SLC6A1
Childhood-onset epileptic encephalopathy (COEE)	CHD2
Juvenile myoclonic epilepsy (JME)	CACNB4, CLCN2, EFHC1, GABRD, GABRA1

Among the mentioned genetic factors, recent literature highlights the significance of SCN1A, SCN2A and CHD2 genes in influencing the risk of DRE. Candidate genes such as MDR1/ABCB1, CYP2C9, CYP2C19, and mutations leading to the dysfunction of receptors sensitive to benzodiazepines also deserve attention. The most important findings from recent years are discussed below (Figure 1). It is probable that the mentioned genetic factors may change the

pharmacodynamic and pharmacokinetic properties of the drugs used. The polymorphisms of some microsomal enzymes (CYP2C9, CYP2C19) and genes encoding P-glycoprotein are consistent with the pharmacokinetic hypothesis, while variants of genes encoding GABA receptors (GABA$_A$) and ion channels may determine disturbances in pharmacodynamic functions.
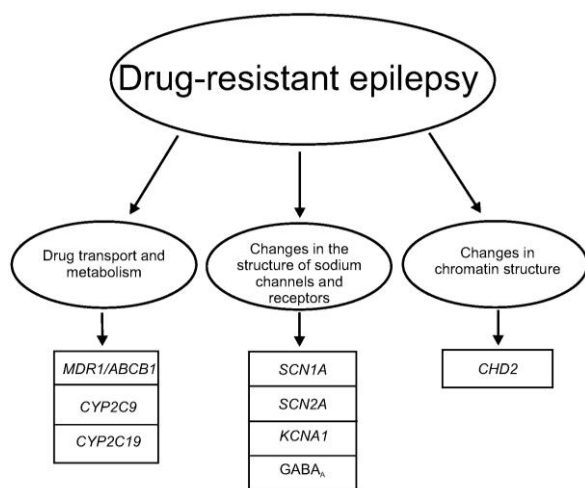

Fig. 1. Main factors involved in drug-resistant epilepsy etiology.

Mutations in SCN1A *and* SCN2A *genes encoding the α subunit of sodium channels*

Sodium channels are multi-subunit membrane proteins responsible for initiating action potentials, among other functions, in nerve cells.

The genes *SCN1A* and *SCN2A* encode the α subunit of voltage-gated sodium channels, and thus mutations in these genes may be a potential source of drug resistance in epilepsy [22,23].

To date, over 1800 mutations have been identified in the *SCN1A* sequence, with over 95% arising *de novo* [34]. Mutations in the *SCN1A* gene, occurring in most patients with Dravet syndrome [35], are also significant in the pathogenesis of DRE with generalized tonic-clonic seizures. These mutations are heterozygous in nature [36], which is understandable in the context of *de novo* or dominantly inherited disorders. Nonetheless, a study of four children with early infantile epilepsy revealed two homozygous missense mutations (Met400Val, Arg618Cys), suggesting the need to consider the *SCN1A* gene even in cases of suspected autosomal recessive neurological disorders [35].

Interesting insights have also emerged from studies examining whether *SCN1A* gene polymorphisms determine an individual's response to antiepileptic drugs and whether they may predispose to the occurrence of DRE in children. Researchers demonstrated that in the intronic regions of the analyzed gene, heterozygosity for the AC polymorphism rs6730344, homozygosity for the AA polymorphism rs6732655, and homozygosity for the AA variant rs10167228 potentially increase the risk of drug resistance (OR = 1.58; OR = 2.25; OR = 1.89; p < 0.05) [37]. The latest literature also indicates that the polymorphic variants of the *SCN2A* gene may influence different responses to antiepileptic treatment.

The AG genotype of rs2304016 in *SCN2A* was more frequent among Chinese patients resistant to valproic acid (VPA) compared to patients responding to the drug (OR = 3.18; 95%CI = 1.10–9.14; p = 0.032). Moreover, in the subgroup of focal seizures, a lower frequency of VPA resistance was observed in heterozygotes AG rs2298771 *SCN1A* compared to homozygotes AA (OR = 0.11; 95%CI = 0.01−0.91; p = 0.040) [38]. Furthermore, studies conducted in the Pakistani population revealed that patients with poor seizure control had significantly higher frequencies of the 56GA and 56AA variants of the *SCN2A* gene than the seizure-controlled group (χ^2 = 14.4; p = 0.0007) [39]. Analyses of 218 Chinese patients suggested an association between the rs17183814 polymorphism of *SCN2A* and higher maintenance doses of oxcarbazepine in patients with a lower body weight and lower maintenance doses of oxcarbazepine in overweight patients [40]. Similarly, another study of 201 Chinese patients treated with VPA showed an association between the s230416 *SCN2A* polymorphism and response to VPA (OR: 0.302; 95%CI: 0.126–0.721; p = 0.007), as well as interactions between the rs17183814 *ABAT* and rs1641022 *SCN2A* variants, which may play a significant role in the pharmacological mechanism of VPA (p = 0.006) [41].

As demonstrated above, there is significant genetic variability in determining the phenomenon of drug resistance in the course of epilepsy/epileptic syndromes in children.

Mutations in the gene encoding chromodomain helicase DNA-binding protein 2

The *CHD2* gene encodes the DNA-binding chromodomain helicase 2 protein, which plays a crucial role in chromatin structure remodeling. Mutations in this gene may predispose individuals to various developmental disorders, including epilepsy and autism spectrum disorders [42]. The majority of described *CHD2* mutations arise *de novo* [43]. Recent studies have identified 15 previously unknown *CHD2* mutations associated with the phenotypes of the Lennox-Gastaut syndrome, West syndrome, myoclonic-astatic epilepsy, and nonspecific epileptic encephalopathy. Among 17 analyzed patients, 8 experienced treatment-resistant seizures [44].

In addition, recent observations have identified a *de novo* nonsense mutation in the *CHD2* gene in a boy with epilepsy displaying characteristics of juvenile myoclonic epilepsy. Genome sequencing ultimately revealed a nonsense mutation involving the substitution of cytosine with thymine in the long arm of chromosome 15. This identified mutation determined the epilepsy phenotype and drug resistance [45].

Polymorphisms of genes encoding P-glycoprotein and cytochrome P450 enzymes

The *MDR1/ABCB1* gene encodes P-glycoprotein, which plays a significant role in the transport of antiepileptic drugs across the cell membrane. Previous studies suggest that *MDR1/ABCB1* gene polymorphisms contribute to changes in P-glyco-protein activity, thereby disrupting the transport of pharmaceuticals to the brain [46,47].

One of the commonly occurring polymorphic variants of the *MDR1/ABCB1* gene is C3435T. It has been demonstrated that there is an association between C3435T *MDR1/ABCB1* genotypic variants and drug resistance among children in the European population (CC vs. TT: OR = 1.47; 95%CI: 1.00–2.18; p = 0.05); (C vs T: OR = 1.23; 95%CI: 1.0–1.51; p = 0.04) [47]. These findings are consistent with recent studies involving Polish pediatric patients. The analysis involved 271 children: 106 with DRE, 67 with epilepsy responsive to pharmacotherapy, and 98 healthy children. It was found that the C3435T polymorphism may be associated with the manifestation of DRE (p < 0.05). The children who did not respond to pharmacotherapy were characterized by a higher frequency of the CC genotype and the C allele carrier status compared to the treatment-responsive group. Conversely, the T allele appears to be a protective factor. However, the authors noted that caution should be exercised in interpreting the results as the observed relationship had not been reported in earlier studies [48]. On the other hand, studies on the Chinese population revealed that genotypes CT (χ^2 = 6.165; p = 0.013) and TT (χ^2 = 11.121; p = 0.001) of the C3435T polymorphism, as well as homozygosity TT (χ^2 = 5.776; p = 0.016) of the G2677T variant, were significantly more frequent in drug-resistant patients [49]. Meanwhile, in a group of Tunisian patients, homozygosity for TT and carriage of the T allele of the C3435T, G2677T, C1236T *MDR1/ABCB1* polymorphisms were found to modulate the body's response to applied antiepileptic treatment [50]. Inconsistencies in the results of the selected reports may arise from factors such as different ethnic backgrounds or heterogeneous criteria for selecting populations for studies.

In the context of drug resistance, attention is also drawn to the *CYP2C9* and *CYP2C19* genes, which encode cytochrome P450 enzymes involved in drug metabolism. Polymorphisms in these genes can lead to varied sensitivity of the body to the therapeutic dose of a drug. An analysis conducted in the Polish population revealed that carrying the T allele of the rs1799853 polymorphism in the *CYP2C9* gene can increase the risk of drug resistance in children with epilepsy fourfold (OR = 4.00; 95%CI: 1.79–8.94; p = 0.0003).

Studies investigating the potential role of polymorphisms in selected genes highlight the significant role of genetic background in shaping the risk of DRE. Nevertheless, owing to the high cost of genetic analyses, these studies are not considered a standard diagnostic procedure [51].

Mutations in benzodiazepine-sensitive receptors

Benzodiazepines (BDZ) are commonly prescribed as anxiolytic, sedative, and anticonvulsant medications. They have a wide range of applications in the prophylaxis of epileptic seizures in patients with DRE [52].

Polymorphic variants in different subunits of the $GABA_A$ receptor affect the number, structure, and function of the receptor. Recent reports indicate two frameshift variants in the α1-3 and 5 subunit domains of the $GABA_A$ receptor: NM_000807.4(GABRA2):c.367_368insG and NM_000810.4(GABRA5):c.410del, which result in premature stop codon formation. This may lead to benzodiazepine resistance in patients with diagnosed epilepsy [53]. Earlier literature also underscores the role of reduced benzodiazepine binding in the epileptic focus [54]. In addition to the R43Q and K289M polymorphisms in the γ2 subunit [55,56], a number of other variants have been identified [57,58,59,60,61], the cumulative effects of which appear to lead to $GABA_A$ receptor dysfunction and alterations in benzodiazepine binding dynamics [53].

Other factors predisposing to refractory epilepsy in children

Another risk factor that may predispose to the development of refractory epilepsy is alterations in the gut microbiota composition. Available literature has demonstrated the connection between the central nervous system and the gut microbiome, forming the brain-gut axis. The relationship between the central nervous system and the gastrointestinal tract is bidirectional as the brain communicates with the gut through neurotransmitters and bioactive mediators that influence the gut microbiota composition. Micro-organisms in the gastrointestinal tract maintain gut

eubiosis, controlling bacterial overgrowth. This plays a particularly significant role in shaping gut homeostasis by affecting the gut immune system, regulating the production of gut hormones, fermenting dietary polysaccharides, and influencing energy acquisition. Simultaneously, changes in gut microbiota composition can impact the state of the central nervous system and the liver due to their close anatomical and functional relationship. The human intestine harbors 100 trillion microorganisms, and the mass of gut microbiota is approximately 2000 g. Notably, the number of microorganisms exceeds the total number of cells in the human body [62].

Dysbiosis (also known as dysbacteriosis) is defined as an imbalance or improper adaptation of gut microorganisms. Furthermore, dysbiosis encompasses any alterations in gut microbiota composition, signifying a reduction in beneficial microbiota, uncontrolled overgrowth of pathogenic microbiota, a decrease in species diversity, and individual microbiota changes compared to other individuals. Dysbiosis disrupts local homeostasis and contributes to various pathological conditions, such as Parkinson's disease, autism spectrum disorders, anxiety disorders, depression, and neurodegenerative diseases [63,64,65,66].

Gut microbiota is a dynamic structure of microorganisms, including bacteria, viruses, fungi, archaea, and eukarya, collectively referred to as the "second human genome" [67]. The composition of gut microbiota is individual and depends on various factors such as the mode of delivery, gender, age, diet, physical activity, stress, past infections, pharmacotherapy including antibiotic use, alcohol consumption, tobacco smoking, and diurnal variability [68]. Among these, diet is a major modulator of the diversity and species richness characterizing healthy microbiota. Approximately 90% of gut microbiota consists of three bacterial types: Firmicutes, Bacteroidetes, and Proteobacteria, while the remaining 10% belong to Verrucomicrobia, Actinobacteria, and Fusobacteria [69]. The abundance of bacteria in the intestine increases from the proximal to distal parts, with anaerobic bacteria predominating in the colon (Table II). Their composition also changes in different parts of the gastrointestinal tract.

Table II. Bacterial density in various parts of gastrointestinal tract

Stomach	Jejunum	Duodenum	Ileum	Colon
10^2 CFU/ml	10^3 CFU/ml	10^{3-4} CFU/ml	10^{7-9} CFU/ml	10^{10-12} CFU/ml

Analyses comparing the gut microbiota composition in patients with refractory epilepsy to those with DRE reveal significant differences. It has been demonstrated that patients with refractory epilepsy have an enriched flora of rare bacteria, mainly from the Firmicutes phylum. Furthermore, among patients experiencing seizures less than 4 times a year, an increased number of Bifidobacteria and Lactobacillus bacteria have been discovered, suggesting a potential protective role against epilepsy occurrence [70]. There are also speculations that gut microbiota, by regulating the levels of neurotransmitters such as serotonin, norepinephrine, dopamine, GABA, and glutamate, participates in the pathogenic mechanisms of refractory epilepsy and associated depression [71]. Researchers hypothesize that changes in the microbiota composition impair the synthesis and metabolism of ATP-binding cassette (ABC) transporters, thereby playing a significant role in the pathogenesis of treatment-resistant epilepsy [70,72].

Another newly considered risk factor that may predispose to the development of refractory epilepsy is the immune mechanism [73]. Autoantibodies have been identified as an underlying cause of unexplained DRE, and a link between autoimmunity and epilepsy has been suggested [74]. Besides the lowered seizure threshold caused by inflammation, a direct epileptogenic role has been approved for many of those autoantibodies, especially those targeting neuronal extracellular antigens [75].

Diagnosis of refractory epilepsy

The diagnostic process for refractory epilepsy should encompass five stages. The first stage involves a comprehensive description of seizure semiology. The second stage entails identifying the type of seizures, with information from the patient and their close contacts proving valuable. The third stage focuses on classifying the diagnosed epilepsy into a specific epileptic syndrome. The fourth stage serves to determine the etiology of the epilepsy through diagnostic assessments. In the final stage, the impact of the observed epilepsy on the overall development of the patient is analyzed [76].

One fundamental and diagnostically valuable test is EEG [76]. This test aids in identifying seizure types and their triggers. It is important to consider the appropriate frequency range of brain waves and EEG limitations (a normal recording does not rule out epilepsy). To enhance the sensitivity of the test, it should be conducted during the patient's sleep or shortly after a seizure. Video-EEG is also of significant importance in diagnosing refractory epilepsy, especially when standard procedures fail to identify the condition or when surgical treatment is being considered [76,77].

Another imaging modality used in the diagnosis of refractory epilepsy is magnetic resonance imaging (MRI). In patients with treatment-resistant epilepsy, experienced radiologists perform this test according to specific protocols. During the examination, the radiologist searches for structural brain abnormalities that could be causing refractory epilepsy [76,77].

Other methods, such as single-photon emission-
-computed tomography (SPECT) and positron
emission tomography (PET), allow functional
assessment of the patient's brain cortex and the
potential identification of epileptogenic foci [76].
The role of genetic diagnostics should also be
emphasized. The ILAE recommends performing
genetic testing as a detailed diagnostic step following
basic evaluations [19]. The following techniques are
employed to diagnose the genetic basis of refractory
epilepsy: microarrays, next-generation sequencing
(NGS), whole genome sequencing, exome sequencing,
and panel sequencing [19,78].

Treatment of DRE

The treatment primarily revolves around pharmaco-
therapy. When selecting the appropriate therapeutic
approach, the type of epilepsy and the classification
into first, second, and third-line drugs should be taken
into account. The medication form should be tailored
to the patient's age. The potential for interactions with
other medications taken by the child should also be
considered [79]. During pharmacotherapy,
medications with identical mechanisms of action
should not be combined. This applies, among others,
to drugs like carbamazepine and phenobarbital, which
block sodium channels [77]. Other drugs used in
epilepsy therapy include VPA, phenytoin,
oxcarbazepine, lamotrigine, gabapentin, clonazepam,
vigabatrin, and lacosamide [23]. In certain situations,
rufinamide therapy has been successful. Analyses
have shown that rufinamide use (among children for
whom multiple drugs have not been effective) is safe
and particularly effective among pediatric patients
with Lennox-Gastaut syndrome [80].
Researchers and physicians also hold hope for gene
therapy and alternative methods of drug
administration that could advance the treatment of
DRE. Current gene therapy concepts involve
introducing therapeutic genes using viral vectors into
specific epileptogenic areas of the brain. These
strategies are currently focused on treating focal
epilepsy [81]. In this context, one of the key candidate
genes is *NPY*, encoding neuropeptide Y. It has been
demonstrated that this neuropeptide, through Y2
receptor activation, inhibits epileptic activity in the
hippocampus [82]. Recently, studies on chronic
epilepsy have been conducted using an animal model.
Inducing the disease by implanting kainic acid into the
hippocampi mimicked the development of chronic
temporal lobe epilepsy in humans. Analysis revealed
that unilateral recombinant gene therapy based on
rAAV-NPY/Y2 administration into the epileptic focus
reduced seizure frequency by $79.0 \pm 23.6\%$ in all the
tested animals compared to the pre-treatment period
($p < 0.05$) [83]. Additionally, the relevance of
considering neuropeptide Y in antiepileptic therapy in
humans was confirmed by the in vitro studies of
epileptic tissue obtained from treatment-resistant
temporal lobe patients. Similar efficacy was not
observed with the use of galanin [84]. Attention is also
drawn to the modified gene encoding the voltage-
-gated potassium channel KCNA1, which, when
placed in a lentiviral vector, reduced the frequency of
seizures in the neocortex of rodents with focal
epilepsy [85].
In the discussed therapy, substances that support or
enhance the action of antiepileptic drugs are also
utilized. Selected experimental studies suggest that
cannabinoids may exhibit antiepileptic effects.
However, the use of medical marijuana in epilepsy
treatment remains a controversial issue. Therapy
involving medical marijuana carries the risk of
numerous adverse effects, which may outweigh the
potential benefits. Furthermore, the positive results
from its application often stem from unconfirmed
sources. Therefore, further research is needed to
investigate the effectiveness of this therapy and to
determine the optimal form, dosage, and tolerance of
cannabinoid preparations [86].
In the treatment of DRE, surgical methods can be
considered in specific situations, among which
restrictive and palliative approaches are distinguished.
In the first group, we include: lobectomy (mainly
removal of the temporal lobe or parts thereof, less
commonly involving other lobes), hemispherectomy
(resection of the entire cerebral hemisphere), and
lesionectomy (the removal of epileptic foci). Palliative
methods include corpus callosotomy (involving
sectioning of the corpus callosum) and deep brain
stimulation, as well as vagus nerve stimulation [8].
To qualify a patient for surgical treatment, a compre-
hensive diagnostic assessment is necessary. Imaging,
electrophysiological, and neuropsychological tests are
required [77]. A significant role in this process is
played by 18-FDG PET/CT (18-fluorodeoxyglucose-
-positron emission tomography/computed tomo-
graphy), which, compared to commonly used
neuroimaging studies, better defines the extent of the
epileptic focus. It thus allows potential confirmation
of the indication for surgical treatment [87]. Recent
reports also demonstrate the effectiveness of treating
pediatric patients with DRE in the tuberous sclerosis
complex using responsive neurostimulation (RNS)
systems. Observations of five RNS patients showed
a median reduction in seizure frequency of 86%
and no complications related to implantation or
stimulation [88].
Among the non-pharmacological and adjunctive
methods for treating DRE, the ketogenic diet is also
noteworthy. In this diet, 90% of calories come from
fats, mainly medium-chain fatty acids. The remaining
calories are allocated to carbohydrates and proteins.
There are several modifications of this diet [89], but

there are no definitive reports on which one is the most effective [90]. Further research is needed to develop metabolic profiles for patients with DRE to specify the necessary dietary restrictions. Available literature states that implementing the ketogenic diet among children with DRE in the context of tuberous sclerosis may reduce seizure frequency by 50% [91]. The efficacy of the diet has also been studied in children diagnosed with Lennox-Gastaut syndrome, where a reduction of over 50% in seizure frequency was observed [92]. In children with Dravet syndrome, the ketogenic diet has a similar efficacy to standard polytherapy [93].

Based on existing data, it can be inferred that the ketogenic diet is an effective non-pharmacological method to support the treatment of DRE as it can not only reduce seizure frequency but also enhance the effectiveness of polytherapy itself [89].

A recent meta-analysis also indicates the favorable impact of the modified Atkins diet, which may contribute to reducing seizure frequency while showing better tolerance compared to the ketogenic diet [94].

Recently, the treatment of DRE through the elimination of dysbiosis has gained importance. The link between gut dysbiosis and epilepsy occurrence has led to increased interest in modifying gut microbiota. For this purpose, therapy involving probiotics can be used. According to the WHO definition, probiotics are live microorganisms that, when administered in adequate amounts, confer health benefits to the host. The use of probiotic bacteria improves the function of the gut endothelial barrier and increases the genetic diversity of the microbiota. In one study it was demonstrated that probiotic-inclusive therapy enhances the quality of life for epilepsy patients and has a positive impact on seizure control [95]. Preclinical studies conducted on an animal model have shown that probiotic supplementation yields a beneficial effect, resulting in a reduced epilepsy phenotype and improved cognitive function in the studied animals [96].

Selected complications of pediatric DRE

DRE can lead to numerous complications, among which the risk of premature death in children stands out. This risk particularly affects children who do not experience disease remission. In a 40-year cohort study of 245 children with epilepsy, as many as 60 of the observed patients died. This rate was three times higher than the expected mortality rate in the general population [97].

Due to the phenotype characteristics of the discussed disease entity, injuries are also common complications. A long-term study analyzing the frequency of injuries resulting from epileptic seizures in children showed that the most common injuries were wounds requiring sutures (30%). Fractures (19%) or tooth injuries (14%) ranked second in terms of frequency, followed by concussions, burns, and dislocations of the shoulder joint. Children with epilepsy that progressed without remission ($p < 0.0001$) or exhibited drug resistance ($p < 0.0001$) were particularly susceptible to these injuries [98].

One of the significant complications includes drug-induced liver injury (DILI). This is especially relevant in cases of DRE, where multiple drugs are used concurrently (in combinations) or sequentially. DILI refers to liver damage caused by the interaction of a drug with liver cells, leading to biochemical disturbances, a clinical symptom complex, and changes in liver histopathology [99]. In Western Europe and the United States, half of DILI cases progress to acute liver failure, resulting in either liver transplantation or patient death. There is a lack of definitive data on this in Poland. According to current knowledge, the severity of liver damage is influenced by genetic factors, including cytochrome P polymorphisms, drug acetylation, patient age, diet, the concomitant use of multiple drugs (dexamethasone, carbamazepine, phenytoin), substances, and the coexistence of liver diseases.

Drug reactions can be divided into two main types [99,100]: dose-dependent hepatotoxicity and idiosyncrasy (non-allergic hypersensitivity). In the first type, the mechanism of damage is directly related to the toxic action of the drug, and the extent of organ damage depends on the single or cumulative dose. A characteristic feature is an increase in aminotransferase activity. Among antiepileptic drugs, VPA may exhibit the discussed pathomechanism. The second type of drug reaction is characterized by complete unpredictability in the relationship between the extent of liver damage and drug dose. In hepatocytes, abnormal metabolites accumulate, and in the case of idiosyncrasy, phenytoin may be a causative factor. Some authors also distinguish a third type, an allergic reaction, dependent on polymorphisms in the HLA system. In this case, the most common symptoms are skin changes accompanying liver damage.

Furthermore, based on the duration of the damage, liver injury can be classified as acute (up to 3 months) or chronic (over 3 months) [99]. In terms of the site of liver cell damage, it is classified as parenchymal (a very high increase in aminotransferase, high hyperbilirubinemia), cholestatic (a high increase in cholestasis enzymes), or mixed [99]. Cholestatic damage may be induced by carbamazepine, while liver inflammation may be caused by phenytoin.

The main symptoms of DILI include nausea, vomiting, a loss of appetite, fatigue, abdominal pain, itching, jaundice, and symptoms of acute liver failure.

In the diagnosis of DILI, it is crucial to establish a relationship between liver damage characteristics and the administered drug(s). Therefore, a thorough medical history should be collected, analyzing the drugs used, their dosage, and the duration of pharmacotherapy. It is also essential to conduct chronological laboratory tests, taking into account the potential coexistence of other liver diseases. Diagnostic tools such as drug discontinuation tests and re-exposure tests are also used. Ultimately, liver biopsy is performed to establish a diagnosis. The most important aspect of DILI treatment is discontinuation of the suspected liver-damaging drug [101]. For causal treatment, levocarnitine is recommended in VPA-induced cases. Additionally, symptomatic treatment is used: ursodeoxycholic acid for cholestasis, cholestyramine, colestipol, antihistamines, naloxone for itching, and corticosteroids for allergic-type DILI. Liver transplantation is indicated in cases of acute liver failure [102].

It is worth mentioning that epilepsy leaves a profound impact on the mental health of children and adolescents. Patients often experience sadness and frequently struggle with depressive states. Seizures can evoke feelings of embarrassment and shame. The disease limits their social life and hinders forming relationships. Children with epilepsy often feel isolated and disconnected from their surroundings. They also suffer from low self-esteem. Moreover, many of them experience memory and concentration problems, which in turn affect their learning abilities [103,104].

Conclusions

Advancements in genetic and clinical research have led to the identification of new predisposing factors for the manifestation of DRE among children. Nonetheless, further analyses are necessary to better understand the multifactorial background of this discussed medical condition. In the future, this could potentially facilitate the integration of genetic tests into clinical practice, resulting in a more accurate selection of therapeutic methods personalized to each patient's individual response.

Funding

Author's contribution

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Manuscript preparation – M. Knopek, J. Iwanicka, G. Boryczka
Literature research – M. Knopek, J. Iwanicka, G. Boryczka
Final approval of the version to be published – J. Iwanicka, G. Boryczka

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