Epilepsy diagnosis and treatment in children – new hopes and challenges – literature review

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Abstract

Introduction and Objective. Epilepsy is one of the most commonly diagnosed neurological aberrations. Epileptic seizures are the main symptoms of the condition. Reducing the seizures is the main objective of the treatment. The aim of the review is to summarise current knowledge on diagnosis and various treatment methods of epilepsy among children.

Review Methods. Scientific publications in PubMed, Google Scholar, Wiley Library, Web of Science, Clinicaltrials.gov, and NCBI databases were searched for the review. More than 93% of the articles are less than eight years old. After an initial assessment of articles, meta-analyses and reviews on epilepsy, concerning the pharmacological, surgical, and gene therapy of epilepsy, were selected. Publications were analyzed using a non-systematic review method to create a brief synthesis of the information.

Brief description of the state of knowledge. Diagnosis of epilepsy consists of subjective and objective examination of the patient and performing electroencephalography. Additional procedures, such as neuroimaging of the central nervous system, genetic testing, metabolic and immunological tests, may expand the diagnostic stage. Pharmacological methods prove that early initiation of treatment reduces the risk of relapse. First-line pharmacological treatment consists of carbamazepine, valproic acid, oxcarbazepine, and phenytoin. If epilepsy proves to be drug resistant, surgery is an alternative.

Summary. The review emphasizes the development of currently used diagnostic methods, therapeutic options, and importance of further research.

Key words

epilepsy, pharmacological treatment, surgical treatment, gene therapy, diagnosis

INTRODUCTION AND OBJECTIVE

Epilepsy is one of the most common neurological conditions which occurs in approximately 0.5–1% of children worldwide. However, it is not a disease entity but a syndrome of symptoms that can occur against various morphological and metabolic changes in the brain. One of the symptoms of epilepsy is epileptic seizures, i.e., temporary bioelectrical disturbances in the nerve cells of the brain. The simplified classification of epileptic seizures distinguishes between generalized seizures and partial (focal) seizures, depending on other things, on the area of the brain where the discharges occur. Determination of the epileptic syndrome, i.e., the specific set of seizure types and electroencephalographic and imaging features, is the final stage of diagnosis [1–2].

The cause of epilepsy is very often not recognized, and for this reason the diagnosis should be based on a thorough history of the patient, witnesses to the seizures, electroencephalogram (EEG) studies, and structural and functional neuroimaging of the central nervous system [3–4].

The aim of the review is to present the diagnostic and therapeutic process of epilepsy and show new pathways in treating this disease and its potential impact.

REVIEW METHODS

This review is based on scientific publications in PubMed, Google Scholar, Wiley Library, Web of Science, Clinicaltrials.gov, and NCBI databases. More than 93% of the articles are less than eight years old. After an initial assessment of articles, meta-analyses and reviews on epilepsy, pharmacological epilepsy treatment, epilepsy gene therapy, and epilepsy surgical treatment were selected. Publications were analyzed using a non-systematic review method to create a brief synthesis of the available information. The countries included in the analysis were mainly developed countries. The age of respondents ranged from 0–18 years.

BRIEF DESCRIPTION OF THE STATE OF KNOWLEDGE

Diagnosis of childhood epilepsy. According to the current International League Against Epilepsy (ILAE) definition, a diagnosis of epilepsy can be made if a child has had at least 2 unprovoked epileptic seizures more than 24 hours
apart in their life, one unprovoked epileptic seizure with a probability of having another seizure at risk after a second seizure within the next 10 years, or if a specific epileptic syndrome is diagnosed [5].

Of most significant importance in the diagnosis of epilepsy is an early subjective and objective examination by a specialist epileptologist and video recordings of the seizure, if they exist. It is important to obtain information about the type of seizure from eyewitness accounts [6]. In children and adults with a first unprovoked seizure, it is reasonable to perform an EEG to determine the risk of recurrence and possible diagnosis of epilepsy or epileptic syndrome [7], which also follows the recent recommendations of the American Academy of Neurology [8]. Performing an EEG is recommended as soon as possible after a seizure, preferably up to 72 hours [6], although some studies suggest no more than 16 hours [9]. This test alone cannot be used to diagnose epilepsy; it is a test to confirm the diagnosis, but it must be remembered that it should not be used to exclude the diagnosis of epilepsy. It is recommended that provocative maneuvers be performed during the EEG examination [6], which, when examining patients with absence of seizures, translates into placing the patient into a state of hyperventilation in a sitting position, which in studies in 2020 was associated with better detection of abnormalities [10].

After a seizure, it is also essential to perform an ECG and other tests to identify metabolic abnormalities – mainly measuring glucose tests to differentiate epilepsy from other conditions, e.g. hypoglycaemia. The National Institute for Health and Care Excellence (NICE) committee, from which these recommendations are derived, does not see the need for serum or imaging tests to make the primary diagnosis but stresses the importance of these tests to find the cause and clarify the diagnosis [6]. Magnetic resonance imaging (MRI) of the brain should be performed in any child with unprovoked, new-onset seizures, especially if sedation is not required. The International League Against Epilepsy emphasizes the need to consider etiology at every stage of diagnosis, including structural etiology, which is best assessed by brain MRI to help classify a possible epileptic syndrome [11]. Obtaining a negative image on MRI is an indicator for single-photon emission computed tomography (SPECT) imaging, which is also helpful in identifying an epileptogenic focus before performing surgery to treat drug-resistant epilepsy [12–13].

According to the ILAE, conditions that can cause a seizure also include pre- and peri-natal trauma, other injuries, strokes, and central nervous system (CNS) infections, including parasitic infections [14]. The occurrence of seizures against a background of CNS infection can be confirmed by performing a lumbar puncture. An elevated temperature, leukocytosis, and pleocytosis in the cerebrospinal fluid may also be present in an epileptic state, despite the absence of CNS infection [15]. The American Pediatric Society (AAP) guidelines for the medical management of children and adolescents with febrile convulsions, do not suggest routine diagnostic testing, including lumbar puncture, unless the condition warrants it. When ruling out CNS bleeding or trauma, imaging studies should be performed. Computer tomography once played a role in the evaluation of patients with epilepsy but is now considered a second-tier imaging modality. Its main advantage is its high sensitivity in detecting calcifications which can occur in some phakomatoses [16], and its usefulness in detecting intracranial haemorrhage, tumours, and brain infarcts [17].

In 2017 and 2022, the ILAE published an updated classification of epilepsy and epileptic syndromes which take into account the age of the patient [18–20]. More accurate diagnosis of epilepsy varies depending on the suspected etiology, and uses ancillary tests such as neuroimaging, genetic and metabolic tests, and immunological tests for this purpose. A three-step disease identification model has been proposed, including diagnosis of the type of epileptic seizure (focal, generalized, and unknown), type of epilepsy (focal, generalized epilepsy, complex generalized and focal epilepsy, and epilepsy of unknown group), and possible epileptic syndrome [18].

To diagnose generalized epilepsy, an EEG recording indicating generalized spike-wave activity is usually needed. People with generalized epilepsy can have many types of seizures: absence seizures, myoclonic, atonic, tonic, and tonic-clonic seizures. Generalized epilepsy is diagnosed based on clinical symptoms, supported by the finding of typical interictal discharges in the EEG. Caution should be exercised in patients with generalized tonic-clonic seizures and regular EEG recordings. A standard interictal EEG recording does not exclude the diagnosis of epilepsy [21]. Confirmatory evidence, such as a significant family history or myoclonic seizures, would be required to make the diagnosis of generalized epilepsy.

Focal epilepsies can be divided into single and multifocal, and seizures involving one hemisphere. Among focal seizures, on the other hand, one can distinguish between conscious or impaired consciousness, motor or non-motor focal seizures, and focal or bilateral tonic-clonic seizures. The interictal EEG usually shows focal epileptiform discharges, but the diagnosis is made based on clinical symptoms which are supported by the EEG findings [18]. Careful analysis of the paroxysmal EEG and corresponding seizure semiology on video can help distinguish focal from generalized epilepsy [22].

There is also a group of complex generalized and focal epilepsies, as some patients have both generalized and focal seizures. The diagnosis is also made based on clinical symptoms supported by EEG findings. Seizure recordings are helpful but optional. An interictal EEG can show both generalized waveform discharges and focal epileptiform discharges, but epileptiform activity is not required for diagnosis. Examples of epilepsies in which both types of seizures occur are Dravet syndrome and Lennox-Gastaut syndrome. The term ‘unknown’ is used to describe a situation in which a patient is presumed to have epilepsy. However, the doctor is unable to determine whether the type of epilepsy is focal or generalized because there is insufficient information, or the EEG recording was normal [18].

According to the ILAE definition, an epileptic syndrome is a characteristic set of clinical and EEG features, often supported by specific etiological findings (structural, genetic, metabolic, immunological, and infectious). When defining epileptic syndromes in newborns and infants, the focus is on the electroclinical picture, with a detailed description of the type of seizures, relevant antecedents, neurological examinations, comorbidities, and interictal and seizure EEG patterns. Most syndromes have a characteristic seizure type or types and often it is second-tier EEG features necessary for diagnosis [19].

Most generalized epileptic syndromes that begin in childhood have a genetic etiology [20]. Recent ILAE
recommendations indicate that genetic evaluation should be performed at the third level of epilepsy diagnosis, for which infants with epileptic seizures and patients of all ages should be referred after the failure of a single antiepileptic drug [23]. Genetic tests, such as next-generation sequencing (NGS) and microarrays, are used for this purpose [24–26]. Traditional Sanger sequencing is time-consuming and targets a single gene, but it is highly accurate and less expensive than newer alternatives. Next-generation sequencing (NGS), or massively parallel sequencing, enables the rapid sequencing of large numbers of DNA segments that are separated into smaller pieces, sequenced and resequenced, and analyzed computationally. NGS has made it possible to study large panels of genes, whole exome sequencing (WES), or whole genome sequencing (WGS) [25]. Genetic testing is not recommended for drug-responsive epilepsy or at the onset of epilepsy. However, comparative genomic hybridization (CGH) can be used for first-level evaluation of patients with global developmental delay, a population at higher risk for epilepsy. Metabolic testing should be performed at the onset of epilepsy in infants in whom a structural cause of seizures has not been detected [26]. If indicated, initial biochemical testing should be performed for the rapid detection of treatable metabolic abnormalities, pending confirmation of a genetic cause. At the same time, genetic evaluation can be initiated using microarrays, followed by a gene panel and then WES if a diagnosis is still sought [27].

Suspicion of metabolic epilepsy requires biochemical tests and, if the diagnosis is not established, genetic tests as well as tissue biopsies. Biochemical tests include blood glucose levels, electrolytes (calcium, magnesium), lactate, arterial blood gasometry, urinary ammonia, and ketones. Biochemical screening should determine plasma carnitine and acylcarnitine, amino acids, and urinary organic acid profile [27]. The ILAE, on the other hand, recommends that serum glucose, sodium, potassium, and chloride levels, ammonia determination, arterial blood gasometry, liver tests, and urinalysis be performed first [26].

The concept of immune-mediated epilepsy is that it results directly from a disorder of the immune system, manifested by inflammation of the central nervous system, with an autoimmune basis. Diagnosis of these autoimmune encephalitis is based on antibody tests. Examples include encephalitis directed against the NMDA (N-methyl-D-aspartate) receptor and encephalitis required against LGI1. With the emergence of these disease entities, this etiological subgroup deserves a separate category, especially given the therapeutic implications for targeted immunotherapies [18].

At present, there is no adequate tool for predicting second epileptic seizures. For this reason, the NICE committee believes that a research recommendation should be made for its development and testing [28]. Abnormal neuroimaging findings have been identified as a risk factor for recurrence after a first seizure. Focal seizures have a higher risk of recurrence than generalized seizures because they are most often associated with structural etiology, abnormal EEG recordings, and neuroimaging findings. An analysis of 18 studies according to the ILAE Subcommittee for Paediatric Neuroimaging guidelines showed that 50% of imaging studies in children with new-onset epilepsy and localization-related or remote symptomatic seizures are abnormal. In a study evaluating neuroimaging in children with new-onset status epilepticus seizures, 8.5% had intracranial pathology.

The etiology of distant symptoms (traumatic brain injury, perinatal trauma, stroke, CNS infection), epileptiform activity on EEG, nocturnal seizures, and potentially epileptogenic changes on brain imaging, are also associated with a high risk of second epileptic seizures [7].

Imaging is vital in determining the risk of a subsequent seizure. Additional tests other than MRI are often necessary to assess the exact location of epileptic foci, especially when there is no concordance between imaging findings and clinical data of EEG recordings. A non-invasive testing technique for localizing epileptogenic brain areas, especially in focal epilepsies with negative MRI results, is 18F-Fluorodeoxyglucose positron emission tomography (PET) imaging. A typical symptom in patients with epilepsy is a regional decrease in glucose uptake (hypometabolism) in the interictal state [16]. Currently, radionuclide imaging, such as PET and SPECT, is not used in the primary diagnosis or evaluation of epilepsy of recent onset. However, it can play an essential role in certain specific situations, such as non-invasive pre-operative localization of epileptogenic brain areas in patients with refractory epilepsy seizures in whom epilepsy surgery is being considered [12]. PET and SPECT can play an essential role in the evaluation of various epileptic syndromes, especially those of unknown cause, revealing various underlying abnormalities. In other cases, these neuroimaging modalities preclude surgery and can help guide the decision to use genetic testing [29].

Magnetoencephalography (MEG), as a non-invasive neuroimaging technique, is also mainly used to localize epileptogenic foci in patients with drug-resistant epilepsy. It is characterized by very good temporal resolution, allowing high-frequency brain activity to be recorded [30]. MEG is also a promising diagnostic biomarker for differentiating between focal and generalized epilepsy due to differences between resting MEG connectivity. However, more studies are needed to include magnetoencephalography as a diagnostic modality for epilepsy [31].

Only a few studies on using microRNA and BDNF neurotrophin as diagnostic biomarkers for epilepsy have emerged. Researchers point to the possibility of using microRNAs as diagnostic and prognostic biomarkers for various diseases, including epilepsy. However, the studies conducted are not thorough enough and do not include a large study group to currently consider microRNAs during diagnosis [32–34]. Among neurotrophins, BDNF has received the most attention due to its possible role in the development of numerous neurological and psychiatric disorders. Due to its lack of specificity, however, its utility may be limited to monitoring response to treatment, with no potential for use as a marker signaling disease onset [34]. The diagnostic process of epilepsy has been summarized in Figure 1.

Pharmacological treatment of epilepsy. Pharmacological treatment of epilepsy is a long-term process. It requires determination of the appropriate dose of the drug affecting the course of the disease. The aim is to control seizures by using the lowest possible effective dose of the agent. Randomized studies in adult and paediatric patients have shown that early initiation of treatment reduces the risk of relapse. Treatment is usually given on its own, as multiple drugs may affect the therapeutic concentration of one substance. The efficacy of pharmacological antiepileptic therapy depends, among other things, on the selection of the appropriate therapeutic
regimen for the type of seizure occurring in the patient. When selecting a drug, the pharmacological profile and adverse reactions of the substance should be considered. If a given drug fails to achieve the therapeutic goal, a second preparation is introduced gradually. Combination therapy should be considered if 2 monotherapies have failed. Epilepsy may be considered drug-resistant if seizure control has not been achieved despite the use of at least 2 appropriately selected and properly administered antiepileptic drugs. For drug-resistant patients, there are options for surgical treatment, diet, and neurostimulation. Withdrawal of antiepileptic drugs should be gradual to avoid the occurrence of severe seizures or epileptic conditions [35–39]. During pharmacological treatment, drug concentrations should be monitored. This practice is crucial in pregnant patients after the addition of a new drug, and in the assessment of the relationship between adverse reactions and drug levels [36].

The main pharmacological agents, often used first, are carbamazepine, valproic acid, oxcarbazepine and phenytoin. Other drugs used in the treatment of epilepsy are vigabatrin, lamotrigine, feldamc, gabapentin, levetiracetam, ethosuximide. The mechanisms of action of these drugs are summarised in Table 1 [36,40]. The results of one of the most comprehensive meta-analyses, published in the Cochrane Systematic Review Database, indicate that carbamazepine is an appropriate first-line treatment option for patients with focal seizures. Carbamazepine is also used in generalised, tonic-clonic seizures as a second-line treatment. In cases of resistance to monotherapy, it is used in multi-drug treatment. The results of a systematic review and meta-analysis show that although some of the new antiepileptic drugs are better tolerated, none of the drugs studied was the most effective [41–42]. A study in 43 European countries showed that carbamazepine was the only drug available in all European countries studied [43]. It is a potent inducer
Phenytoin

Inhibition of intracellular sodium currents. Reduces the influx of calcium ions into the cell. Inhibition of motor cortex and subcortical centres responsible for the tonic phase of convulsions.

Carbamazepine

Blocks potential-dependent sodium channels and secondary reduction of glutamate release and catecholamine metabolism in the central nervous system. Stabilisation of the membrane of over-excited nerve fibres. Inhibits repetitive neuronal discharges and reduction of synaptic transmission of excitatory stimuli.

Lamotrigine

Inhibits sodium channels and blocks release of excitatory amino acids (glutamic acid).

Oxcarbazepine


Topiramate.

Blocks membrane voltage-dependent sodium channels, increases gamma-aminobutyric acid activity, and shows antagonism to the receptor for glutamic acid.

Gabapentin.

Inhibits voltage-gated calcium channels.

Pregabalin.

Binds to an auxiliary subunit (α2-δ protein) of the membrane voltage-shifted calcium channel in the central nervous system.

Levetiracetam.

Affects protein concentrations in neurons by partially inhibiting N-type calcium currents and reducing the release of calcium ions stored inside neurons. In addition, the drug partially abolishes the zinc- and beta-carboline-induced inhibition of currents gated by gamma-aminobutyric acid and glycine. The drug binds to synaptic vesicle protein 2A, which is involved in vesicle fusion and exocytosis of neurotransmitters.

Vigabatrin.

Selective, irreversible inhibitor of γ-aminobutyric acid aminotransferase (GABA-T).

Valproic acid.

Selective enhancement of enzyme activity involved in the synthesis of gamma-aminobutyric acid (GABA) and inhibition of GABA-degrading enzymes. Stabilisation of the cell membrane by affecting voltage-dependent sodium channels. The drug also affects rod calcium T-type channels.

Felbamat.

Demonstrates GABA inhibitory activity and benzodiazepine receptor binding.

Lacosamide.

Attenuation of low-threshold T-type calcium currents in thalamic nerve cells.

Ethosuximide.

Blocking of T-type calcium channels. Inhibitory effect on thalamic neurons.

Table 1. Mechanisms of action of antiepileptic drugs [35–50]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
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<tr>
<td>Ethosuximide</td>
<td>Blocking of T-type calcium channels. Inhibitory effect on thalamic neurons.</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Binds to an auxiliary subunit (α2-δ protein) of the membrane voltage-shifted calcium channel in the central nervous system.</td>
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</tr>
<tr>
<td>Levetiracetam</td>
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of liver enzymes, which can lead to significant interactions with other medicinal products [44].

Oxcarbazepine is a structural analog of carbamazepine, and like carbamazepine, blocks sodium channels. Therefore, the monitoring of serum sodium is recommended, mainly if there are risk factors for hyponatraemia. Oxcarbazepine has been shown to be a much weaker inducer of liver enzymes than carbamazepine, making it less susceptible to drug interactions. The drug is used in monotherapy or combination treatment in adults and children over 6 years of age [42].

Valproic acid is used in patients with generalized and unclassified epilepsy, but should be avoided in women of childbearing potential due to its teratogenic effect. Valproic acid is metabolized in the liver, therefore, if used, liver function tests are recommended. It is an inhibitor of liver enzymes which may lead to increased concentrations of concomitant medicinal products, such as carbamazepine, phenytoin, or lamotrigine [36–37,45–48]. It is crucial to select the appropriate lowest effective dose of phenytoin. Its elimination decreases dramatically with increasing dose, which may lead to the development of toxicity. Intravenous phenytoin is the drug of choice for the treatment of status epilepticus or recurrent focal epileptic seizures and for the prevention of epileptic seizures after neurosurgery [36].

Lamotrigine is used for the treatment of focal and generalized tonic-clonic seizures [36]. It is relatively one of the best drugs dedicated to pregnant women, as it is associated with the lowest risk of severe congenital disabilities. However, no drug used to treat epilepsy appears to be entirely safe for the developing foetus. Lamotrigine is used for the treatment of simple and complex partial seizures and generalized seizures in adults and children over the age of 12, both as monotherapy and as adjunctive treatment. [37]

Gabapentin and vigabatrin are excreted unchanged by the kidneys and do not interact with other medicinal products. Particular attention should be paid to vigabatrin and felbamate, which carry a risk of retinopathy [36,40]. Felbamat can cause aplastic anaemia and severe hepatitis, and is most commonly used in patients who respond poorly to other medicines. Gabapentin is used as monotherapy or as adjunctive therapy in focal seizures. Vigabantine is a drug used in the combination treatment of focal epileptic seizures, or in the monotherapy of epileptic seizures in infants (West’s syndrome – flexion seizure syndrome) [37].

In the treatment of epilepsy, ethosuximide has a narrow therapeutic profile. It is the drug of choice in monotherapy or combination therapy in children with generalised absence epilepsy (petit mal). Thalamocortical rhythms are involved in the generation of pulse-wave discharges, which are the characteristic electroencephalographic signs of absence seizures. Spontaneous activity of thalamocortical circuits involves low-threshold T-type calcium currents in the thalamus, and ethosuximide is thought to reduce these low-threshold currents in thalamic neurons. The observed side-effects of ethosuximide are dose-dependent and involve the gastrointestinal tract and central nervous system [38–39].

Levetiracetam binds to the synaptic vesicle protein SV2A, interfering with the release of neurotransmitters stored in the vesicle – thus selectively accumulating and inhibiting rapidly activating neurons. Levetiracetam also inhibits N-type potassium and calcium channels. This drug is used as adjunctive therapy for focal or generalised myoclonic and tonic-clonic seizures and as monotherapy for seizures. Efficacy and tolerability compare favourably with other antiepileptic drugs. Levetiracetam has few drug interactions [49–50].

Proper treatment requires an accurate diagnosis of the type and syndrome of epilepsy. When choosing the appropriate therapy, patients should be approached individually, and when selecting the proper treatment regimen, the effectiveness and safety of using a particular preparation should be taken into account.
Surgical treatment of epilepsy. If drug-resistant epilepsy (DRE) is diagnosed, surgery is an alternative to pharmacotherapy. Studies have shown the positive impact of early surgical intervention on cognitive function and, thus, further intellectual development in paediatric patients [51]. Depending on the etiology of the seizures, resection, separation, or neurostimulation procedures are used.

Among resective operations, the most common procedure involves the temporal lobe, with the most common being anterior temporal lobectomy (ATL), which is more effective in reducing the incidence of seizures, than selective amygdalohippocampectomy [52]. Resection operations focus on the treatment of focal cortical dysplasia, mesial temporal lobe epilepsy (MTLE), and local lesions [53]. In the treatment of MLTE, the structures of the limbic system are removed: amygdala, hippocampus, parahippocampal gyrus [54].

Resections of the frontal, parietal, and occipital lobes are much less frequent. Local lesions responsible for seizures may be dysplasia outbreaks, cavernous angiomas, and primary tumours, such as hypothalamic hamartoma or gliomas. Lesionectomy is aimed at removing such local pathologies, and their accurate localization before surgery is the first stage of preparation for resection.

In the pre-operative location of epilepsy foci, EEG is used, the great advantage of which is that it is non-invasive and offers the possibility of repeated examination. However, its effectiveness may not be sufficient for extra-temporal changes. To increase the chances of detecting foci requiring resection, electrodes directly adjacent to brain tissue are used in an invasive electroencephalogram (iEEG) [55–56]. A system of electrodes inserted into the cerebral pulp at the site where the source of epileptic seizures is sought continuously monitors the brain’s bioelectrical function and thus creates a stereo EEG (sEEG).

In addition to operations requiring craniotomy, neuroablation techniques are also available to ensure a lower invasiveness of the procedure, including radiofrequency thermocoagulation (RFTC) and Laser Interstitial Thermal Therapy (LITT). The goal of RFTC is denaturation within the epileptic outbreak, resulting in less frequent seizures. The studies examined the use of RFTC under the control of sEEG imaging to localize the resective lesion more effectively. One to four electrodes left for the duration of the procedure, in close proximity to the sought epileptic focus, are called the ‘guiding electrodes’ [57–58]. However, it should be noted that temporal lobe lobectomy maintains a higher percentage of post-operative seizure reduction in the treatment of temporal lobe epilepsy [59]. Patients who had undergone sEEG-RFTC surgery required re-operation with classical lobectomy, which allowed them to achieve more satisfactory treatment results. Based on the results of the studies, it can be concluded that sEEG-RFTC is a good alternative for hard-to-reach lesions located within the limbic system, and a less effective technique for temporal lobe outbreaks [60].

Magnetic resonance-guided laser interstitial thermal therapy (MRgLITT) also avoids craniotomy by inserting a laser diode implant through a small hole in the skull. This is associated with less invasiveness of the procedure and shorter patient stays in hospital [61]. Ablation can be performed in an ordinary operating theatre and is a promising technique for epilepsy in the case of a hard-to-operatively access lesion, particularly in paediatric patients. It is essential to develop further studies comparing the cost-effectiveness ratio of open surgical methods and techniques using thermoablation [62–63]. Studies indicate challenges related to the ablation of epilepsy foci located in the islet, which anatomically presents poorer accessibility, which also affects the ineffectiveness of EEG in localizing the resection area. Using the MRgLITT technique, satisfactory results of surgical treatment were achieved after applying a wide ablation margin [64].

Resective procedures are the most effective and are therefore referred to as therapeutic procedures, whereas some detachment techniques and neurostimulation can only reduce the number or effects of epileptic seizures, without removing the root cause, leading to them being referred to as palliative methods. It should be noted that the boundary between therapeutic and palliative interventions in the context of drug-resistant epilepsy is blurred and depends on the individual patient.

Achieving a complete absence of seizures is unlikely in most drug-resistant patients. The techniques used in palliative care aim to reduce the frequency, extent, and duration of seizures in order to achieve the highest possible quality of life [65].

For epilepsy involving a large portion of the cerebral cortex, multifocal epilepsy, or epilepsy with seizure propagation, it is necessary to separate the mating fibres that pass through the corpus callosotomy (CC). The aim of the operation is to break the fibres through which the discharges responsible for the propagation of the epileptic seizure, referred to as ‘drop attacks’ spread. Partial or total CC can be performed as part of the procedure [66]. Callosotomy, which has been used since the 1940s, is an effective palliative treatment of multifocal drug-resistant epilepsy with secondarily generalized seizures. The operation thus contributes to limiting developmental regression, which is a complication of frequent epileptic seizures [67]. Callosotomy is a good form of treatment for diseases such as early infantile epileptic encephalopathy [67]. Traditionally, callosotomy assumes craniotomy, but in recent years, a trend has been observed to use neuroablative techniques to reduce the invasiveness of the procedure [66]. This retrospective study compared the efficacy of open anterior CC (involving the anterior 2/3 of the corpus callosum), total CC, and CC using LITT. The study group consisted of patients who underwent a single operation in the period 2003–2021 and were classified for CC based on the following criteria: drug-resistant epilepsy (failure of ≥ 2 antiepileptic drugs), and absence of a well-localized epileptic focus [68]. Efficacy results were similar in both CC with craniotomy and LITT, with no significant differences in re-assessment at 6, 12, and 24 months using the Engel classification [66].

<table>
<thead>
<tr>
<th>Outcome class</th>
<th>Definition</th>
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<tr>
<td>Class I</td>
<td>Free from seizures</td>
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<tr>
<td>Class II</td>
<td>Rare seizures (≥75% reduction)</td>
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<tr>
<td>Class III</td>
<td>Significant improvement (≥50% reduction)</td>
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<tr>
<td>Class IV</td>
<td>No significant improvement</td>
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For large brain tumours, cortical dysplasia involving a large area of the hemisphere, or polio with paraplegia or hemispheric paralysis, the surgical method of choice is hemispherectomy. Anatomical hemispherectomy is distinguished, which involves...
resection of the cortex and disconnection of the entire hemisphere from the rest of the brain. In this form, surgery was introduced, and although it presented effective prevention of epileptic seizures, the procedure is associated with late complications, such as hemispheric paraplegia, limited field of vision, or hydrocephalus [68–69]. Later, a less extensive functional hemispherectomy with separation of hemispheric tissue and preservation of occipital and frontal cortex was proposed, which has been shown to be equally effective in controlling seizures while reducing late complications. The surgery may be performed using a variety of strategies, including Modified Functional Hemispherectomy, Perinsular Hemispherotomy, Parasagittal Hemispherotomy, Endoscopic-Assisted Hemispherotomy [68]. The effectiveness of the procedure for acquired epilepsy is much higher than for the etiology associated with developmental disorders leading to dysplasia [70].

For a drug-resistant patient who is not eligible for surgical treatment or who has not had satisfactory results, neurostimulation is an alternative. Vagus nerve stimulation (VNS) is a procedure that is effective for both focal and generalized epilepsy. Initially, it was used only in adults and older adolescents, but can now be safely used in adults and paediatric patients [71]. According to the ILAE recommendations, VNS should be considered after careful assessment of eligibility for surgical treatment [72]. The therapy can be used in any age group, regardless of the type of epilepsy. The technique involves implanting a stimulator, and an electrode coming out of it wrapped directly around the left vagus nerve in the cervical section. Positioning the electrode on the right side would be associated with a higher risk of arrhythmia due to the effect of the right vagus nerve on the atrial-ventricular node of the stimulus-conducting system of the heart [73–74]. Stimulation is associated with potential side effects, among which can be distinguished cough, hiccups, dysphagia, and hoarseness associated with excitation of the posterior laryngeal nerve [75].

Another commonly used technique from this group is deep brain stimulation (DBS). In patients with generalized epilepsy, the most common site of stimulation with the use of DBS is the medial nucleus of the helix. Stimulation of the heap is designed to inhibit the propagation of the epileptic seizure, or even inhibit the primary arousal. This procedure is particularly promising in the case of Lennox-Gastaut syndrome, where the central nucleus of the hill is considered to be the dominant point for development of an epileptic seizure [76].

Comorbidity in children with epilepsy. Children with epilepsy often have a comorbidity, which can be divided into neurological, psychiatric, and somatic comorbidity (Tab. 3) [77–80].

Table 3. Comorbidities in epilepsy [73–76]

<table>
<thead>
<tr>
<th>Neurological comorbidities</th>
<th>Psychiatric comorbidities</th>
<th>Somatic comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speech disorders</td>
<td>Autism spectrum disorder</td>
<td>Loss of bone mass</td>
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<tr>
<td>Cognitive impairment</td>
<td>Attention deficit hyperactivity disorder</td>
<td>Immune disorders</td>
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<tr>
<td>Migraines</td>
<td>Depressive and anxiety disorders</td>
<td>Growth retardation</td>
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<tr>
<td>Sleep problems (nocturnal sleep, daytime sleepiness, and parasomnia)</td>
<td>Suicidal thoughts and tendencies</td>
<td>Polycystic ovarian syndrome</td>
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</tbody>
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- Striperentol – increases the activation time of GABAA receptors and release of GABA. Clinical studies have proven the effectiveness of striperentol in the treatment of Dravet’s syndrome. Side-effects include drowsiness, decreased appetite, and arousal [81–83].

Gene therapy. One of the most rapidly developing methods of pharmacological therapy for treating diseases; drugs currently in the laboratory phase. Gene therapy involves placing foreign genetic material into a patient’s cells, resulting in one of 3 options: inhibiting production, of the gene, increasing production of the gene, or modifying the site of the gene [80]. Potential points of action of gene therapy in epilepsy and its mechanism are shown in Table 4 [85–87].

One of the newer possible therapeutic options now is the treatment of loco-resistant epilepsy with cannabinoids (CBD), derived from the cannabis plant. In 2018, CBD was approved for use by the United States Food and Drug Administration for treating Dravet syndrome and Lennox-Gastaut syndrome in patients aged two years and over. The mechanism of the anti-seizure action of cannabis (also called marijuana) is not precisely known. In the phase 3 GWPCARE2 clinical trials in patients with Dravet’s syndrome after CBD, a 46–49% reduction in seizures was observed at 10 or 20 mg/kg/day, compared to placebo, where a 27% reduction was observed. In patients with Lennox-Gastaut syndrome in phase 3 GWPCARE4 clinical trials, 44% were observed at 20 mg/kg/d compared to 20% in the control group. This shows that CBD significantly reduces the number of seizures. Side- effects include somnolence, fatigue, and diarrhea [88–90].

Another promising treatment option for epilepsy is the ketogenic diet. Increases in GABA, adenosine, and noradrenaline and a decrease in glutamate in nerve synapses are considered potential modes of action of the diet. Other factors affected by the ketogenic diet are inhibition of histonic deacetylases, improvement of mitochondrial function, and reduction of oxidative stress. Studies, including a meta-analysis by Martin-McGill et al., have shown that in children with drug-resistant epilepsy, using the ketogenic diet significantly reduced seizures. A reduction in seizures was obtained in almost 85% after 3 months on the diet, and about 50% achieved a complete absence of seizures. The main side-effects of the diet were diarrhea and constipation. The child must be tested for fatty acid transport and oxidation disorders before introduction [91–93]. In adults, the ketogenic diet does not produce such good effects because the decrease in the number of seizures after about 3 months is maintained in only 10% of patients.
The use of CBD and the ketogenic diet are currently among the new therapeutic methods. Other methods, such as gene therapy for epilepsy, are currently largely in the laboratory testing phase, but offer promising possibilities in treating and eliminating symptoms of drug-resistant seizures. In the case of the above-described drugs, all of them are used in the treatment of severe, often drug-resistant epileptic syndrome, e.g. Dravet syndrome and Lennox-Gastaut syndrome, in which the symptoms appear in early childhood. CBD therapy is a new option with confirmed effectiveness and helps reduce the frequency of seizures in Dravet syndrome and Lennox-Gastaut syndrome. The ketogenic diet is a promising new method for treating epilepsy, but further research is needed to confirm the effectiveness of this method [81–93]. All the drugs mentioned provide the opportunity for patients to improve their quality of life.

**SUMMARY**

The diagnostic and therapeutic process of epilepsy is currently a major challenge for doctors. A thorough patient interview, patient observation, EEG examination, structural and functional neuroimaging allow for a diagnosis that directly impacts the selection of appropriate, personalized treatment.

The review emphasizes the development of therapeutic possibilities in treating epilepsy and assisting in the improvement of the quality of life of patients with the disease. The review also indicates the need for doctors to update their knowledge of the methods currently available.

**REFERENCES**

Epilepsy diagnosis and...
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