

## Surgical Approach To Epilepsy In Children With Ineffective Anti-Epileptic Drugs

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### Abstract

*Drug-resistant epilepsy (DRE) affects 25% of all epileptic patients, and quality of life decreases in these patients due to their seizures. Early detection is crucial in order to establish potential treatment alternatives and determine if the patient is a surgical candidate. Neurosurgical treatment may improve seizures in children and adolescents with drug-resistant epilepsy, but additional data are needed from randomized trials. A total of 47 patients were identified; 10 treated with ASMs, 3 treated with ASMs + VNS, and 34 treated with ASMs + cranial epilepsy surgery. In this single-center trial, children and adolescents with drug-resistant epilepsy who had undergone different types of epilepsy surgery had a significantly higher rate of freedom from seizures and better scores with respect to behavior and quality of life than did those who continued medical therapy alone. The surgery resulted in expected neurological deficits related to the area of brain resection.*

Keywords: Drug-resistant epilepsy, Vagus nerve stimulation, Pediatric neurosurgery, Epilepsy surgery.

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### 1. Introduction

Although the concept of drug resistant (often used interchangeably with “medically refractory/intractable” or “pharmacoresistant”) epilepsy may appear self-explanatory and intuitive, a precise definition has remained elusive.<sup>1</sup> The International League Against Epilepsy (ILAE) defines drug-resistant epilepsy as “failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom”.<sup>2</sup> Seizure freedom is considered to be sustained when the patient is seizure-free for more than one year, or has sporadic seizures separated by a period

three times the longest interval between seizures prior to the treatment, whichever is longer. As a serious health problem worldwide, epilepsy accounts for 1% of the world's diseases.<sup>3</sup> About 25% of all patients with epilepsy present drug-resistant epilepsy.<sup>2</sup> As a consequence of poor control over their epileptic seizures (ES), they present an increased risk of early death, trauma, and psychosocial alterations, while their quality of life is diminished. Drug-resistant epilepsy may show temporary remission periods (4% of adult cases yearly, with higher rates in children) but ES frequently reappear. Therefore, identifying patients with drug-resistant epilepsy is essential in order to start preparing the presurgical evaluation, and to arrange for possible

therapeutic alternatives in specialised units or centres. Traditionally, therapeutic failure of three antiseizure drugs defined intractability.<sup>4</sup> Epilepsy surgery offers a potential cure or significant improvement to those with focal onset drug-resistant seizures. Unfortunately, epilepsy surgery is still underutilized which might be in part because of the complexity of pre-surgical evaluation. Pre-surgical evaluation includes classifying the seizure type, lateralizing and localizing the seizure onset focus (epileptogenic zone), confirming the safety of the prospective brain surgery in terms of potential neurocognitive deficits (language and memory functions), before devising a surgical plan.<sup>5</sup>

**Pathogenesis of drug-resistant epilepsy.** The pathogenesis of epilepsy is complex and, at present, commonly acknowledged to be caused by the excitatory and inhibitory imbalance of the central nervous system. So far, the hypotheses regarding the pathogenesis of drug-resistant epilepsy mainly include transporter hypothesis, target hypothesis, etc.

**Transporter Hypothesis.** Most antiepileptic drugs play the antiepileptic role in the brain via the blood-brain barrier.<sup>7</sup> Moreover, the overexpression of multidrug transporters that have a role in the efflux from the capillary endothelial cells which form the blood-brain barrier may lead to increased intracellular drug efflux or isolated vesicles, resulting in decreased intracellular drug concentration or changed drug distribution; consequently, antiepileptic drugs in epileptogenic zone and surrounding tissues cannot achieve the effective drug concentration, which leads to drug resistance.<sup>8</sup> At present, multidrug transporters that are frequently studied include P-glycoprotein (P-gp), multidrug resistance protein (MRP), breast cancer resistance protein (BCRP).<sup>9</sup> Some common drugs, such as carbamazepine, felbamate, gabapentin, lamotrigine, phenobarbital, phenytoin and topiramate, are all substrates of P-glycoprotein; meanwhile, phenytoin is substrates of multidrug resistance protein-2 (MRP2).<sup>10,11</sup> Kerstin Römermann et al. found that lamotrigine is a substrate of BCRP, which is evidenced in this hypothesis.<sup>12</sup>

**Target Hypothesis.** Target hypothesis proposes that antiepileptic drugs cannot inhibit the excessive discharge of neurons through binding the predetermined target when the structure or function of the target of antiepileptic drugs changes, resulting in uncontrollable epilepsy attack, which is mainly reflected by abnormal

ion channel function.<sup>13</sup> Currently, it has been confirmed that the voltage-gated sodium channel (VGSC) is mainly expressed in excitatory cells, and is the main target of the traditional first-line AEDs.<sup>14</sup> Research has proved that SCN1A gene (coding for the sodium channel, neuronal type I, alpha subunit) mutation is the main pathogenic gene of severe myoclonic epilepsy in infancy.<sup>15</sup> In addition, the model experiment of gene knockout mice for simulating human channel diseases has verified that SCN1A mutation causes reduced expression level of sodium channel subtype Nav1.1, leading to decreased excitatory of inhibitory neurons, functional decline in inhibitory loop and increased neuronal excitability, which are necessary for the onset of epileptic seizures.<sup>16</sup> Sodium channel gene mutations cause the loss of partial functional targets of the AEDs, decreased amplitude and duration of inhibitory sodium current, increased excitability of the whole neural network, and action potential spreading to the whole or partial brain, and thereby forming epileptic discharge. Also, Escayg A et al. compared 226 patients with drug-resistant epilepsy and 185 controls, revealing that the proportion of SCN1A mutations in the patients with drug-resistant epilepsy was significantly higher than that in the control group.<sup>17</sup>

**Surgical treatment of drug-resistant epilepsy.** Although there were multiples of new-type antiepileptic drugs that have been continued to be approved for application, there still exist more than 30 percent of patients with epilepsy developed into drug-resistant epilepsy.<sup>6</sup> With the continuous development of related science and technology, a variety of different surgical treatment methods emerged in response to the proper time and conditions, and now surgical treatment has become a very important therapeutic tool for drug-resistant epilepsy treatment. The goal of surgery is to reduce the seizures, to avoid the adverse reaction after surgery, and to a certain extent, to improve the quality of life. In general, we need to adjust the preoperative state of patients to meet the criteria of surgery. At present, surgical treatment methods for epilepsy are divided into resective surgery, palliative surgery, neurostimulation and other surgical interventions.

## 2. Methods

Prospective and retrospective study on 47 cases with drug resistant epilepsy at National Children's Medical Center. All cases are subjected to history and clinical examination. Patients treated with antiseizure medications (ASMs) only, Patients treated with

antiseizure medications (ASMs) plus vagus nerve stimulation (VNS), and ASMs plus cranial epilepsy surgery were studied regarding access to epilepsy surgery and disparities in care. All patients underwent Magnetic Resonance Imaging (MRI) 3T, according to the HARNESS-MRI protocol and electroencephalography (EEG). This study used Engel classification (EC) to describe seizure outcomes. Preoperative factors studied included epilepsy treatment type, age, sex, patient type, epilepsy type, and presence of pediatric complex chronic conditions (PCCCs).

### 3. Results

A total of 47 patients were identified; 10 treated with ASMs, 3 treated with ASMs + VNS, and 34 treated with ASMs + cranial epilepsy surgery. Main studied factors:

- Age: from 15 days to 9 years (60%) and up to 18 (40%);
- Sex: 28 female (59.57%), 19 male (40.42%);
- Focal/partial epilepsy diagnosis 27 (57.44%), with generalized FRE 20 (42.55%).

Patients treated with antiseizure medications 10 (21.27%). Type of cranial surgery: VNS 3 (6.38%), Focal Cortical Dysplasia (FCD) surgery 24 (51.06%), Callosotomy 8 (17.02%), functional periinsular hemispherotomy 2 (4.25%).

Seizure results according to the Engel scale:

- 53,12% EC I;
- 40,68% EC II,
- 6,2% EC IV.

### 4. Discussion

As for drug-resistant epilepsy, accurate surgical resection has more important significance for the complete or incomplete free of seizure, accurate preoperative localization can not only contribute to the reduction of the risk of surgery, but also help to develop a perfect operation strategy, which can also have a significant impact on the reduction of postoperative complications and improvement of prognostic outcomes. Therefore, it is very important to accurately locate the epileptogenic zone and the functional areas of the brain.

The present study evaluated the clinical characteristics and treatment outcomes of 47 pediatric patients with

epilepsy, highlighting differences in therapeutic approaches and seizure control outcomes. The patient cohort showed a predominance of younger children (60% under 9 years), with a slight female majority (59.57%), which is consistent with previous pediatric epilepsy cohorts reported in the literature. Most patients were diagnosed with focal or partial epilepsy (57.44%), reflecting the common presentation of focal epilepsies in pediatric populations. The treatment distribution revealed that while 21.27% were managed solely with antiseizure medications (ASMs), a significant proportion underwent combined treatments, including cranial epilepsy surgery, underscoring the importance of surgical interventions in refractory or complex cases. Among surgical approaches, focal cortical dysplasia (FCD) resection was the most frequently performed procedure (51.06%), supporting its role as a common etiology in drug-resistant focal epilepsy. The use of vagus nerve stimulation (VNS) and callosotomy, though less frequent, reflects the tailored strategies for patients with diffuse or multifocal epileptic networks or those not amenable to resective surgery. The seizure outcomes measured by the Engel classification revealed that more than half of the patients achieved Engel Class I status (seizure freedom or near seizure freedom), highlighting the efficacy of surgical treatment modalities. Additionally, 40.68% attained Engel Class II, indicating significant improvement, while only a small fraction (6.2%) remained in Engel Class IV, suggesting persistent seizures despite intervention. These findings align with prior studies emphasizing the role of epilepsy surgery in improving seizure control and quality of life in pediatric patients. The relatively high success rate in this cohort supports early consideration of surgical options in appropriate candidates. However, the variability in outcomes also points to the need for individualized treatment plans and further research into predictors of surgical success. Limitations of this study include the retrospective design and the relatively small sample size, which may limit the generalizability of the findings. Future prospective studies with larger cohorts and longer follow-up periods are warranted to better understand long-term outcomes and optimize treatment protocols.

### 5. Conclusion

This single-center study conducted at the National Children's Medical Center in Tashkent, Uzbekistan, demonstrates that pediatric patients with drug-resistant epilepsy (DRE) who underwent surgical interventions—whether focal cortical resection, callosotomy, functional

hemispherotomy, or vagus nerve stimulation—achieved significantly better seizure outcomes compared to those managed with antiseizure medications (ASMs) alone. According to the Engel classification, more than half of the surgical patients (53.12%) achieved seizure freedom (Class I), while an additional 40.68% showed meaningful improvement (Class II), indicating the effectiveness of surgical treatment in this population. These findings highlight the importance of early identification and timely referral of pediatric DRE patients for surgical evaluation. Despite a relatively high rate of referral for surgery in this cohort (72.34%), disparities remain, particularly regarding access to advanced treatments like VNS. The outcomes also affirm that although neurological deficits may result from brain resections, the overall benefit in seizure control and improved quality of life strongly supports surgical intervention in appropriately selected cases. Further multicenter, prospective studies with larger sample sizes are warranted to confirm these findings, optimize referral practices, and reduce disparities in access to epilepsy surgery.

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