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"Treatment of Severe Epileptic Syndromes"

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'Pharmaco-resistant epilepsies : A review'

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REVIEW ARTICLE

Pharmaco-resistant epilepsies: A review

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Abstract: Despite the availability of numerous effective antiepileptic drugs (AEDs), about one-third of patients with epilepsy continue to have frequent seizures during treatment. There are some factors that have been repeatedly identified as potential predictors of refractory epilepsy. There are several researches to understand the mechanisms of drug-resistance in literature. Drug-resistant epilepsy is often a chronic problem, associated with increased psychosocial and physical morbidity. Identifying clinical predictors for pharmaco-resistant epilepsy early in the course of the disorder may be important for directing patients to an effective non-pharmacologic treatment, such as surgery, ketogenic diet or vagus nerve stimulation.

Key words: **epilepsy, drug resistance**

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Definitions and criteria

Although many types of epilepsy are well controlled, intractable or medically refractory epilepsy affectes a significant number of children who do not respond to antiepileptic drugs (AED)**.** Most patients with AED-resistant epilepsy are resistant to several, if not all, AEDs, despite the fact that these drugs act by different mechanisms. The consequences of uncontrolled epilepsy can be severe, with neuropsychological and psychiatric impairment, and social disability [1]. Considering that epilepsy is one of the most common chronic neurologic disorders, drug-resistant epilepsy is a major social health problem. It is not known why and how epilepsy becomes drug resistant in some patients while others with seemingly identical seizure types and epilepsy syndromes can achieve seizure control with medication Although no single accepted definition exists of drug-resistant epilepsy, different definitions may be appropriate, depending on the type of seizure and epilepsy syndrome and the purpose for which the definition is used [2]. Drug resistance is described as uncontrolled seizures despite an appropriate treatment or a good control of the seizures, but with unacceptable adverse effects [3]. There is no consensus on how the concept of intractability should be defined and several investigators have proposed various definitions, creating difficulties to compare results across studies. Definitions usually include the number of AED failures and the minimal remission or seizure frequency during a specified duration therapy.

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The National Association of Epilepsy Centers has considered epilepsy as pharmacoresistant when seizures do not come under control after 9 months of treatment under the care of a neurologist [4].

Recently Berg et al. [5] defined pharmacoresistant epilepsy in children as the failure of two appropriate AEDs, the occurrence of an average of one seizure per month for ≥ 18 months, and no more than a 3 months seizures free hiatus during those 18 months.The number of AEDs tested depends on the chances of alternative therapies such as ketogenic diet, vagus nerve stimulation or epilepsy surgery. According to Kwan and Brodie [6] patients who did not achieve complete seizures control for 12 consecutive months with the first two or three AEDs were given the predictive diagnosis of refractory or drug-resistant epilepsy. There are other different definitions published in literature: since there is no agreement in the definition of drug-resistance, it is not surprising that a spectrum of criteria for drug resistance is reported. Few studies have examined early predictors of intractability in childhood epilepsy. Kwong et al. [7] defined early predictors of seizures refractoriness: seizures onset in the first year of life, high initial seizure frequency, abnormal neurodevelopmental status, symptomatic etiology. Neonatal seizures and status epilepticus during the neonatal period or accompanying an acute insult were rare; however, when they occurred, the outcome was particularly poor [8]. Cumulative evidences suggest that a patient's response to treatment is determinated by multiple factors. Phenotypic markers can be used to predict refractoriness in patients with epilepsy. These include the type of syndrome, etiology, history of seizure frequency and density, and EEG findings. Some genetic syndromes are most frequently associated with a benign clinical course while others are associated with a worse course. For example, most children with monogenic mutation in KCNQ2 or KCNQ3 are affected by benign familial convulsions (BFC) that typically remit before adulthood. In contrast, juvenile myoclonic epilepsy, which also may arise from single gene mutations, does not remit but is very treatment responsive. Other nonremitting, genetically linked epileptic syndromes include the GEFS+ and cortical dysplasia. Patients with idiopathic generalized seizures were most likely become seizures free compared to patients with generalized symptomatic or cryptogenic seizures. Lesion etiology and localization may be additional risk factors in refractory epilepsy: acquired epilepsy, due to stroke or vascular malformation, seems to be much more treatment responsive than the epilepsies associated with cortical dysgenesis or hippocampal sclerosis. Moreover the incidence of refractory epilepsy could vary depending on the time of the patient disease history: the prognosis of a patient with newly diagnosed epilepsy is much better than one with a more chronic history [9]. It is also important to consider that the response to a new AED depends from the previous AED treatment history. According to Schiller and Najjar [10], a significant minority of patients become seizures-free with the newly administered AED treatment even after failure of one to five past AEDs. In contrast after failure of six or more inefficient AEDs, none of the patients become seizures-free.

Pseudo-resistance

Identifying drug-resistance at an early stage is important to address the patients to alternative therapy, but it is necessary to recognize if the epilepsy is really refractory. Clarifying the reason for the initial failure is important; for example, patients who have had an adverse-effect-inspired withdrawal (idiosyncratic drug reaction) may have the same prognosis as they had when they were first treated [11].

Misdiagnosis of epilepsy is possible, but even when the diagnosis of epilepsy is correct it could be that all events are not seizures, so an accurate description is necessary to ensure that all episodes are really epileptic. Even when the diagnosis of epilepsy isobtained, the classification of the seizures could be wrong because the first presentation is not clear and we have to reconsider the diagnosis every time is possible. Pseudo-refractory epilepsy has to be considered because many factors may determine pseudo-resistance as diagnostic or therapeutic errors, poor compliance, external factors, as well as a combination of these. Therapy adjustment may have a beneficial effect on the pseudo-refractory epilepsy [12].

Remitting-relapsing pharmaco-resistance

AEDs are not able to prevent the development of symptomatic acquired epilepsy, although AEDs are impressively blocking seizures in many patients, currently no evidence exists that they influence the course of epilepsy and prevent pharmaco-resistant epilepsy. A study confirmed that early AED treatment reduces the number of seizures but is not able to improve the course of epilepsy [13]. Drug resistance can occur early or late in the course of epilepsy and often epilepsy follows a continuous or relapsing-remitting pattern. Remission of epilepsy was defined as a seizure-free period of five or more consecutive years; terminal remission was defined as remission at the end of follow-up. Terminal remission could be interrupted from the start of the treatment to the end of follow-up (remitting course) or be interrupted by relapse (remitting-relapsing course). Remission could be followed by reappearance of seizures without any further terminal remission (worsening course). Relapse was defined as the occurrence of repeated seizures after a patient had entered remission of five years or more [14]. There are three hypotheses of drug resistance evolution.

First, in most cases pharmacoresistance is constitutive and it has been fully developed before the first seizure or before the start of AED treatment [16]; however some patients develop pharmacoresistant epilepsy after a good response to early AED treatment. Second, some patients, with easily treatable epilepsy, develop pharmacoresistance years later, requiring epilepsy surgery [15]. Third, drug resistance may remit and reappear in the course of epilepsy or its treatment. These data suggest that in some patients pharmacoresistance may be reversible, at least for a period of several years [15]. Sillanpää and Schmidt [14] examine if different evolutionary patterns of intractability does exist in a large prospective group of patients with childhood-onset epilepsy. They found that half patients will eventually enter terminal remission without relapse and another fifth after relapse. One-third will have a poor long-term outcome in terms of persistent seizures after remission or without any remission. These results indicate that initial success or failure to enter remission is not a reliable indicator of long-term success or failure to achieve remission. Most patients with initial failure to reach remission subsequently turn out to enter terminal remission or remission later in the course of the disorder: presumably, these patients would have been diagnosed pharmacoresistant early in their course, but treatment responsive later [16]. Moreover patients with early remission could turn out to be unable to regain remission after a relapse. Schmidt et al [2] affirm that although in most patients drug resistance seems to have been presented de novo, even before the first AED was started, this is not always the case. In some patients with easily treatable epilepsy, drug resistance seems to develop later, and in a third group, drug resistance appears to remit in the course of epilepsy or its treatment.

These data suggest that any theory for pharmacoresistance needs to take into account

that failure to enter remission may be progressive or reversible in some patients with childhood-onset epilepsy. For these reasons it is important to consider that neurobiologic mechanisms of pharmacoresistance may be different in patients who have never responded to an AED versus those who progressed to pharmacoresistance after they responded initially to therapy. In addition, the mechanisms of reversing pharmacoresistance may differ from those generating pharmacoresistance.

Mechanisms of antiepileptic drug resistance

At the molecular level, marketed antiepileptic drugs reduce the incidence of seizures by effects on voltage-gated sodium channels, on components of the GABA system including $GABA_A$ receptors, the GAT-1 GABA transporter and GABA transaminase and on voltage-gated calcium channels. Recently, several additional molecular targets have been defined, including $\alpha_2\delta$, SV2A and K_v7/KCNQ/M potassium channels [17]. Drugs, in the presence of adequate serum levels, traverse the blood-brain barrier (BBB). CNS activity of AEDs is determined by a multitude of factors, including physical properties, such as lipophilicity, that affect their distribution in different compartments within the CNS. It could be that, in pharmaco resistance, sufficient intraparenchymal AED concentrations are not attained, even in the presence of adequate AED serum levels [18]. Two prevailing hypotheses suggest to explain multidrug resistance in epilepsy; the *transporter hypothesis* affirms that AED levels are decreased at their brain targets because of overexpression of drug efflux transporters, such as P-gp, in epileptogenic brain regions. Restricted access of AEDs to the seizure focus is the result of locally increased expression of drug transporter protein **[**17**,**19]. After the permeation into the CNS parenchyma, drugs have to bind to target molecules to exert their desired action. The second hypothesis of pharmacoresistance (*target hypothesis*) suggests that inherited or acquired alterations in the molecular targets of AEDs cause a reduced efficacy of a given AED at the target in epileptogenic brain regions **[**18, 19]. Epilepsy pharmacoresistance occurs when genetic or disease related changes in drug targets make them less sensitive to AEDs **[**17]. There is evidence for increased transporter expression in seizure foci, as yet, in animal models and in human tissue resected in epilepsy surgery. In rodent model AED-resistant, P-gp expression is increased in epileptogenic brain tissue [20] more than in responsive animals [21], associated with lower brain levels of AEDs [22] and, most importantly, coadministration of the highly selective P-gp inhibitor, tariquidar, reverses AED resistance [23]. Some authors affirm that in order to assess the *transporter hypothesis* in epilepsy patients will be the use of ^{11}C-labeled AEDs and PET to determine if AED resistance is associated with lower brain uptake and increased brain efflux of AEDs [19]. A pilot PET study assessing the P-gp ligand (R)-^{11}C-verapamil by patients with temporal lobe epilepsy (TLE) showed increased brain efflux of this ligand in parahippocampal regions of the ipsilateral hemisphere in five of seven patients [24]. The *target hypothesis* of drug failure is based primarily on studies indicating reduced sensitivity of voltage-gated sodium channels to carbamazepine in epileptogenic brain tissue from patients who were not seizure-free while receiving this AED and underwent resective surgery [25]. However it remains unknown if target alterations in epileptogenic brain tissue from AED-resistant patients alter only the efficacy of carbamazepine or whether they can also affect other AEDs that act at sodium channels or ones that have a different mechanism of action [17]. The experimental results indicate that functionally relevant

alterations in both AED targets and AED transporters exist. Clearly, these mechanisms are not mutually exclusive. It is entirely possible that decreased permeation of AEDs into brain tissue, in sinergy with changes in targets for these drugs, mediate pharmacoresistance. This does not exclude that, for some AEDs, predominant mechanisms underlying pharmacoresistance to these drugs can be identified [18]. Furthermore, there is insufficient data to prove either the transporter or target hypotheses of multidrug resistance. The transporter hypothesis, which has a solid base in experimental epilepsy, needs more evidences from human epilepsy studies. The target hypothesis, although intuitively attractive, is based on very few studies in human epilepsy with only carbamazepine [17, 19]. More studies on drug target changes have been used to develop new drugs for the treatment of epilepsy; information on specific resistance mechanisms might also be used to guide potential treatment with drug transporter inhibitors in conjunction with AEDs.

Genetics of antiepileptic drug resistance

Since some years, the researchers have concentrated their attention on the target of antiepileptic drugs and their transport away from the targets, but others approaches have been considered; one is the role of genetics or genomics [26] to understand the disease biology that could lead to newer and more specific treatments. Variation in a single gene may account for or contribute to drug resistance. SCN1A is, currently, the most clinically relevant of all the known epilepsy genes. There has been remarkable progress in understanding epileptogenic pathophysiology in association with mutations in SCN1A causing epilepsy. Mutations in SCN1A can result in a variety of epileptic syndromes, including generalized epilepsy with febrile seizures plus (GEFS+), Dravet syndrome and some other rare epileptic encephalopathies. Whereas seizures in GEFS+ may often be controlled with antiepileptic drug, Dravet syndrome is an intractable epileptic encephalopathy presenting in the first year of life, noted for its pharmaco-resistance and frequent need for polytherapy. Genetic complexity is a possibility for research into genetic causation of epilepsy and drug resistance. Drug resistant epilepsy has been associated with mutations in many other genes, either with epilepsy as the only manifestation, or as a part of a broader phenotype. When such mutations are identified, when definition of related phenotype spectrum, new opportunities arise to explore mechanisms of drug resistance, with the possibility that such mechanisms might be more broadly applicable [27]. Mutation in the X-linked CDKL5 gene can cause severe epileptic encephalopathy in male and female infants, sometimes with a Rett syndrome-like phenotype or with infantile spasms. Recognition of compatible phenotypes is important for a genetic diagnosis, outcome, counseling and for possible future genetically directed treatment options [28]. Early infantile epileptic encephalopathy with suppression burst, also known as Ohtahara syndrome, is one of the most severe forms of epilepsy. It has recently been linked to mutation of the STXBP1 gene: haploinsufficiency seems to be the molecular pathological mechanism, but for this gene mutation and their related conditions, we are far from understanding the basis both of epileptogenesis and drug resistance [29]. Drug-resistant absence and myoclonic seizures associated with an EEG pattern of generalized paroxysmal activity, a marker of idiopathic generalized epilepsies (IGEs), can be a phenotype associated with deficiency of the glucose transporter, Glut-1. Early identification of children with Glut-1 deficiency is important, as seizures are poorly controlled by drugs, though the ketogenic

diet, providing an alternative cerebral energy source, leads to improved control [30].
These are only some examples of drug resistant epileptic syndromes, but this is a promising area of research. Apart the progress in understanding SCN1A-mutation-related epilepsies, there are a lot of works to take possession of mechanisms underlying epileptic syndromes and drug resistance.

Non-pharmacological therapies

Alternative therapy has to be considered in drug-resistant epilepsy. Actually, there are three possibilities leading to improvement in seizures and, in some cases, to delivery, such as epilepsy surgery, vagus nerve stimulation (VNS), ketogenic diet. The Commission on Neurosurgery of the International League Against Epilepsy (ILAE) formed the Pediatric Epilepsy Surgery Subcommission in 1998 with the aim to formulate minimal standards for epilepsy surgery in childhood [31]. In the last years, increasing consensus has grown on the efficacy of surgery to treat drug-resistant focal epilepsy in children [32]. The criteria for epilepsy surgery are [33]: frequent or severe seizures interfering with patient's life; intractable seizures despite appropriate antiepileptic drugs with adequate levels; origin of seizures from a single focus in the brain; removed cortex must be surgically accessible and operable without significant deficit to the patient; complete comprehension of risks and benefits of the procedure must be known by patients and parents. Epilepsy surgery is an efficient option for children with drug-resistant focal epilepsies, and, if the presurgical identification of the epileptic zone is accurate, excellent results are obtained in a considerable amount of cases [34]. In addition seizures control after surgery may result in improvement of developmental, psycosocial and behavioural impairment in children with early-onset epilepsy [31]. VNS received the approval by US Food and Drug Administration (FDA) in 1997 for "adjunctive therapy in the treatment of medically intractable partial epilepsy in people 12 years [35] and older who are ineligible for resective epilepsy surgery" [36]. Although the exact mechanisms of action are unknown, the use of VNS in children has increased, including those younger than 12 years of age [35] or those with generalized epilepsy [37]. As reported by several studies [38] the therapeutic effect of VNS is better in children than in adults and the benefit in children is achieved more rapidly. Moreover the positive response is progressively improved with the time, confirming that the duration of stimulation is the most important factor in clinical long term improvement, due to the cumulative effect of continuous electrical stimulation on the vagus nerve [39, 40]. It is evident that VNS offers substantial therapeutic benefits to some patients only with mild side effects such as cough, hoarseness and voice alteration tend to improve and disappear with time [41]. The ketogenic diet has been used for the treatment of epilepsy in children for almost 100 years [42]. The first modern reports of ketogenic diet were by Guelpha in 1911 and Conklin in 1921. Their hypothesis was that prolonged fasting resulted in detoxification of the gut, giving a decrease in frequency of seizure occurrence. In 1921, Wilder postulated that the antiepileptic effect of the diet was related to the production of the ketones and not to starvation. He proposed that increasing fat content in diet and reducing the carbohydrate would lead to reduction in seizures frequency. In 1927 Talbot developed a ketogenic diet protocol similar to present-diet which consisted of a period of fasting followed by the introduction of 4:1 fat to carbohydrate ratio diet in association with restriction in water intake [43]. The ketogenic diet has been successful tried for the treatment of partial and generalized refractory epilepsy in pediatric patients and it has been suggested as an early option for the treatment of epileptic

encephalopathies, more often associated with severe neurological disorders [44]. There are some adverse effects as vomiting, constipation, drowsiness, gastroesophageal reflux and fever [45], nonetheless, led to the diet's withdrawal only in a small group of patients [46]. How long individuals need to be maintained on the diet remains in question and often is individually assessed. Some children on weaning do not return to their baseline seizure rate. It is commented that patients with 100% efficacy were weaned from the diet. It is not clear at what point and whether improvement was sustained [42].

In conclusion: many questions are opened on pharmacoresistant epilepsy and the researches are engaged to select narrow criteria to understand either the action mechanisms or the best classification to include the correct patients.

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