

Refractory Epilepsy: A Clinically Oriented Review

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Key Words

Neurology • Refractory epilepsy • Epilepsy surgery

Abstract

About one third of patients with newly diagnosed epilepsy do not achieve seizure control despite medical therapy and should be assessed in detail to confirm the diagnosis, to determine the epilepsy syndrome and to plan treatment strategy. Refractory epilepsy is established when there is inadequate seizure control despite using potentially effective antiepileptic drugs (AEDs) at tolerable levels for 1–2 years, and excluding nonepileptic events and poor compliance. An overview of patient management in everyday clinical practice is given. Risk factors for refractoriness include (1) generalized epilepsy with lesions; (2) focal epilepsy with hippocampal sclerosis, cortical dysplasia or hemorrhages; (3) early epilepsy onset; (4) high seizure frequency; (5) absence of response to the first 2 AEDs; (6) high frequency of interictal spikes, and (7) multifocal spikes. The efficacy of surgery ranges from curative (resection) to palliative (vagus nerve stimulation, callosotomy, multiple subpial transections) depending on the epilepsy syndrome and etiology. Using a new antiepileptic drug benefits about one third of patients. Refractoriness is constitutive in most patients and shows a progressive or remission-relapse course in others. As the transporter and target hypotheses do not entirely explain refractoriness, other hypotheses are emerging. New treatments under investigation are described.

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Introduction

In epilepsy, 3 prognostic groups are generally considered: (1) spontaneous remission (20–30%) as seen in benign epilepsy with centrotemporal spikes or childhood absences; (2) remission on antiepileptic drugs (AEDs) (20–30%) as occurs in most focal epilepsy and myoclonic juvenile epilepsy syndromes; (3) persistent seizures under AEDs (30–40%) among which refractory epilepsy is included [1]. Clinical and EEG predictive factors of refractoriness are red flags in the context of epilepsy management and should be thoroughly checked in every epileptic patient. A prompt diagnosis of refractoriness is of paramount importance for a timely selection of patients for surgery. If the epileptogenic zone cannot be resected, palliative procedures should be considered such as vagal nerve stimulation, callosotomy, ketogenic diet or multiple subpial transections. Vagal nerve stimulation and a ketogenic diet achieve a chance of seizure improvement comparable to using a new AED. A better understanding of the mechanisms of refractoriness might contribute to the development of new, more effective AEDs. Refractory patients show an increased risk of psychosocial, psychiatric and medical morbidities that should be readily addressed to ensure a better quality of life [2]. This review aims to be a comprehensive clinically oriented overview of refractory epilepsy, and addresses the following topics: concepts, predictive factors, diagnosis, treatment, natural history, mechanisms and treatments under investigation.

Concepts of Refractoriness

Different definitions of refractoriness emerge depending on the context. All are based on the 3 main components of intractability: number of AEDs previously taken, frequency of seizures and duration of noncontrolled epilepsy [3]. In investigational studies, criteria of refractoriness include: (1) absence of response to 2 AEDs tolerated at reasonable doses; (2) minimum frequency of seizures (e.g. 1 seizure per month) to be considered refractory or the duration of minimum remission (e.g. 6–12 months) to be qualified as nonrefractory, and (3) duration of 1 year to 1 decade of noncontrolled epilepsy. Depending on the criteria applied, the frequency of refractory epilepsy varies from 10 to 37.5% [4–6]. A flexible scale of refractoriness has been developed for clinical use and classifies epilepsy as potential (no seizure freedom with AEDs taken less than 1 year and predictive factors for refractoriness), probable (no seizure freedom more than 1 year with at least 2 AEDs) or definitely refractory (catastrophic epilepsy or no freedom of seizure for more than 1 year after 5 years of treatment with at least 3 AEDs) depending on the duration of epilepsy and medical treatment, seizure control and number of AEDs used [7]. A subclassification of refractoriness as acceptable or unacceptable was also included, taking into account the patients' impression of the impact of epilepsy (seizures, comorbidity and adverse effects of AEDs) on their quality of life (e.g. a patient with acceptable refractory epilepsy presenting infrequent nocturnal seizures may become definitely refractory with the occurrence of diurnal generalized tonic-clonic seizures affecting employment, education and driving). Potential refractory epilepsy may evolve to probably refractory depending on the duration of AED intake and the influence of predictive factors of refractoriness [7].

Predictive Factors of Refractoriness

Epileptic syndrome, response to AEDs, age and seizure frequency at epilepsy onset are clinical determinants for predicting future refractoriness.

A long follow-up study (30 years) of children with epilepsy showed that only 13% of all patients with idiopathic generalized epilepsy, and no case with idiopathic partial epilepsy, were refractory. In contrast, 78% of patients with altogether rare symptomatic generalized epilepsy and 49% of patients with the much more common symptomatic partial epilepsy were not in remission [8].

Typical refractory generalized epilepsy of pediatric ages are the Ohtahara syndrome, early myoclonic encephalopathy (neonatal period), West syndrome, Dravet syndrome (infancy) and Lennox-Gastaut syndrome (early childhood) [9]. In focal epilepsy, hippocampal sclerosis, cortical dysplasia and hemorrhage are associated with refractoriness [10]. The localization of the epileptogenic zone also seems to play an important role in refractoriness. The temporal lobe is probably the most epileptogenic area as it is the most common of the focal epilepsy syndromes [11] and kindling is easily elicited by stimulation of the amygdala [12]. The striate cortex, namely the fourth layer, was also proved to be highly epileptogenic [13]. The motor (hand and face area) and sensorimotor cortices are other areas with low seizure thresholds [14].

Absence of seizure freedom when 2 past AEDs proved inefficient is a crucial predictor of refractoriness [4]. A recent study added that refractoriness is a continuum and showed the benefit of adding a previously not used AED even when 2–5 past AEDs were not effective. Seizure-free rates decreased from 61.8% for the first AED to 41.7% and 16.6% after 1 and 2–5 past AEDs proved inefficient. After 6 AEDs, absolute refractoriness (0% seizure free) was found [15].

A younger age at onset of epilepsy predicts refractoriness [16]. Seizures in the immature brain of a child may result in nonpruning of neurons and contribute to high numbers of gap junctions, which leads to abnormal connectivity, the hyperconnected cortex [17].

High seizure frequency (more than 1 seizure per month) occurring soon after the diagnosis of epilepsy either before or after treatment onset correlates with refractoriness in the short term (2–4 years) and long term (30–35 years) [6]. Depression has recently also been associated with lack of response to AEDs [18]. Neurobiological processes that underpin depression may interact with those producing seizures to increase the extent of brain dysfunction and thereby the likelihood of developing pharmacoresistant epilepsy [18].

Electroencephalography is useful for predicting refractoriness. The quantity of interictal spikes is predictive of severity in temporal lobe epilepsy [19]. Oligospikers, patients with temporal lobe epilepsy with less than 1 spike per hour, correlate with less severe epilepsy [20]. In addition, some studies describe the association between multifocal spikes and intractability [21].

Diagnosis of Refractory Epilepsy

Firstly it is mandatory to exclude false refractoriness related to nonepileptic seizures, inadequate AEDs, non-compliance and seizure-precipitating factors. Video-EEG monitoring is an essential tool in this process, aiming to perform a differential diagnosis of paroxysmal events and a correct classification of seizures and epileptic syndromes. An estimated 20% of patients referred to comprehensive epilepsy programs for medically refractory 'seizures' do not have epilepsy [22]. Nonepileptic events more frequently found include cardiovascular syncope, sleep diseases and psychogenic events [23]. Correct classification of seizure type and epileptic syndrome is mandatory for selecting the adequate AED [24]. Selected generalized forms of epilepsy may be aggravated by some AEDs [24]. Studies have reported that approximately 30–50% of patients with epilepsy do not comply with their prescribed AED therapy [25]. Nonadherence was proved to be associated with a more than threefold increased risk of mortality, a significantly higher incidence of emergency department visits, hospital admissions, motor vehicle accident injuries, and fractures than during periods of adherence [25]. Finally, sleep irregularities, alcohol abuse and specific factors for reflex epilepsy should be excluded.

The second step in the diagnosis of refractory epilepsy is to confirm refractoriness. This definition is generally accepted when there is inadequate control of seizures despite at least 2 potentially effective AEDs (mono- or polytherapy) taken in tolerable doses [26]. Refractory patients should be referred to an epilepsy service for further diagnostic evaluation, optimization of pharmacotherapy, and consideration of other therapies such as epilepsy surgery. The evaluation of refractory patients for epilepsy surgery should consider the following clinical issues: (1) adequate control of seizures should be considered by the patient (e.g. some patients with 1–2 seizures/year prefer surgery for professional or social reasons while others do not feel that seizures have a severe impact on their quality of life) and balanced by the doctor in relation to the probability of successful surgery success compared to AED treatment (e.g. temporal lobe epilepsy with hippocampal sclerosis has such a high probability of seizure freedom that surgery should be considered even with low seizure frequency, in contrast to an extratemporal epilepsy with no MRI lesion where only a high frequency of seizures could justify surgery); (2) although refractoriness is generally considered following 1–2 years of noncontrolled epilepsy, epilepsy surgery may be performed earlier in the case of

catastrophic epilepsy or a high chance of surgical cure, or later in case of low seizure frequency or a very low chance of successful surgery.

Treatment of Refractory Epilepsy

Defining epilepsy refractory to medical treatment implies considering surgery. The prognosis will differ as a function of the epilepsy syndrome and etiology involved and depending on whether the intervention is curative or palliative. In addition, other interventions such as a ketogenic diet and the contribution of AEDs should not be disregarded.

Surgery

Resective surgery is based on removal of the entire epileptogenic area without causing a permanent neurological deficit. The localization of the epileptogenic zone in focal epilepsy is typically based on seizure semiology, interictal and ictal EEG findings, as well as FDG-PET, SPECT and MRI lesions [27]. Focal epilepsy with a lesion not adjacent to the eloquent cortex and concordant with semiology, ictal EEG, interictal EEG and PET/SPECT may be removed based solely on surface evaluation. In the case of focal epilepsy without a lesion, a lesion adjacent to an eloquent cortex or if there is no concordance between the different zones, invasive monitoring is recommended [27].

More than half of the procedures in surgical epilepsy programs are anterior temporal lobe resections [28]. Mesial temporal lobe epilepsy associated with hippocampal sclerosis is the most common form of focal epilepsy, with around 60% of the patients having temporal resection. 60–70% of the patients are free of seizures at 1–2 years of follow-up [29, 30] and only 58% are seizure free at 10 years [31]. The outcome of surgery greatly depends on the underlying cause of epilepsy. Patients with vascular malformations, low-grade tumors, dysembryoplastic neuroepithelial tumors, and cystic lesions have surgical outcomes that are as good as or better than those of patients with hippocampal sclerosis [32]. Cortical dysplastic lesions and post-traumatic gliosis have a 3 times higher rate of recurrence, indicating a risk of incomplete resection or additional epileptogenic areas [33]. Predictors of short-term outcome (duration of epilepsy, age at onset, age at surgery, unilateral spikes, preoperative secondarily generalized tonic-clonic seizures, and preoperative seizure frequency) do not

predict long-term outcome in patients with temporal lobe epilepsy associated with hippocampal sclerosis [34].

Extratemporal lobe surgery for focal epilepsy accounts for less than half of all epilepsy operations [35]. In frontal lobe epilepsy surgery, the probability of becoming seizure free is 55.7% at 1 year, 45.1% at 3 years, and 30.1% at 5 years [36]. The subset of patients with favorable prognostic factors – an MRI lesion restricted to one frontal lobe, complete resection, and a regional or lateralized ictal scalp EEG pattern – show a seizure-free outcome approaching that seen after temporal lobectomy, with 50–60% being seizure free at 3 years. Regarding etiology, patients with low-grade tumors have the best outcome (62%), followed by patients with MRI malformations of cortical development (52%).

Hemispherectomy or hemispherotomy has been reported to be beneficial (improvement of seizure frequency and developmental quotient) in children with catastrophic hemispheric epilepsy of diverse etiologies such as malformations of cortical development, Rasmussen's encephalitis, Sturge-Weber syndrome, and remote vascular insults [37].

Palliative Interventions

Complete seizure control is not a realistic objective for some patients, but useful palliation can sometimes be achieved with techniques such as vagal nerve stimulation, corpus callosotomy, and multiple subpial transections.

Vagal nerve stimulation is indicated in adults with focal epilepsy with no indication of surgery or who had undergone surgery without success and in intractable generalized symptomatic epilepsy. It might also be effective in children with drop attacks and Lennox-Gastaut syndrome. On average, a 50% reduction in seizure frequency has been reported in about one third of patients, the same range of expected benefit as in trying a new AED with the advantage of lower adverse effects. However, seizure freedom is rare [38]. Corpus callosotomy is mostly used in patients with Lennox-Gastaut syndrome to reduce the number of disabling drop attacks [39]. Multiple subpial transections use vertical incisions in the gray matter at 4-mm intervals to limit propagation of epileptic activity within eloquent cortex and to reduce seizure spread without disturbing functional integrity. It is reported to achieve a significant seizure reduction [32]. A ketogenic diet, i.e. high in fat and low in carbohydrate, is mainly used in pediatric patients (due to tolerability) as second-line treatment in focal nonsurgical refractory and gener-

alized symptomatic epilepsy. A recent randomized controlled trial showed a reduction in seizure frequency in more than 50% in 38% of children with drug-resistant epilepsy [40].

In chronic epilepsy (more than 5 years), the addition of a new AED provided a seizure freedom of 17% and a 50–99% seizure reduction of 25%. For those who did not respond to the first trial, a similar benefit might be expected for at least 2 more trials. At the end, 28% of the patients were seizure free [41]. The application of a systematic protocol to the treatment of refractory epilepsy using a new AED might improve seizure control in a substantial proportion of cases. The nihilistic view that intractability is inevitable if seizure control is not obtained within a few years of the onset of therapy is incorrect [41]. Zonisamide, 100–400 mg i.d., levetiracetam, 1,000–3,000 mg i.d., lamotrigine, 300–500 mg i.d., topiramate, 300–1,000 mg i.d., and gabapentin, 600–1,800 mg i.d., have demonstrated efficacy (evidence level A) as add-on therapy in patients with refractory focal epilepsy [42]. Even though the methodology was similar in all studies, it is not possible to determine the relative efficacy from comparison of outcomes because the populations differed, and some drugs were not used in maximum doses whereas others appear to have been administered above the ideal dose. For essentially all drugs, efficacy as well as side effects increased with increasing doses [42].

In refractory epilepsy, it is convenient to perform a systematized management of AED: (1) increase until the maximum tolerable dose; (2) if no response, replace the AED, if there is a partial response, add another AED which should be chosen based on the mechanism of action of the first AED (e.g. lamotrigin and valproate are synergic), its efficacy and adverse effects [24].

Temporal Pattern of Refractoriness

First, based on partly prospective and hospital-based observations in adult-onset epilepsy, it has been claimed that in most cases pharmacoresistance is constitutive, i.e. it is fully developed before the first seizure or at least before the start of AED treatment [4].

There is emerging evidence from one retrospective study of a highly selected group of patients undergoing temporal lobe surgery that, at least in some patients with easily treatable epilepsy, pharmacoresistance requiring surgery developed years later in the course of their epilepsy [43]. If prospective studies confirm these findings and the underlying mechanisms behind these associa-

tions are elucidated, interventions may be envisaged that might interrupt such a process and some day prevent some forms of epilepsy from becoming intractable [44].

Finally, the most controversial hypothesis claims that drug resistance may remit and reappear in the course of epilepsy or its treatment. Some authors have described an intermittent pattern where active epilepsy is interrupted by periods of remission [45]. However, a competing explanation is that the improvement after initial failure to respond may also be related to changes in AED use, for example the introduction of newer drugs, over the years [44].

Natural History

Sillanpaa and Schmidt [46] have studied a cohort of childhood-onset epilepsy for 37 years and found that 33% of patients had refractory epilepsy whereas 67% were seizure free. Most of the refractory patients (27/47 patients) presented as claimed in the constitutive hypothesis of refractoriness from the onset of epilepsy. In the remaining refractory patients (20/47 patients), refractoriness developed later in the course of epilepsy, according to the progressive hypothesis of refractoriness. Although it is reassuring that a total of 67% of patients were able to enter terminal remission, it took more than a decade in many patients, particularly in those with mental retardation and symptomatic epilepsy. A relapse-remission course was seen in 20% of patients while a remission course from the onset of epilepsy was seen in 48% of patients either in the first year (16%) or afterwards (32%) [46]. Further, this study showed that in patients with childhood-onset epilepsy, long-term seizure outcome cannot be reliably predicted by the response at the onset of treatment [46]. This suggests that before initiation of therapy many seizures may be the consequence, rather than the cause, of the underlying physiological mechanism responsible for refractoriness in this group of patients and corroborates the notion that antiseizure drugs do not have a true antiepileptic effect.

Mechanisms of Refractoriness

The transporter and target hypotheses are the most commonly cited mechanisms of refractoriness, although they cannot yet fully explain refractoriness.

According to the drug transporter hypothesis, restricted access of AEDs to the seizure focus is the result

of either locally increased expression of drug transporter proteins, most notably P-glycoprotein (P-gp), encoded by the *ABCB1* gene, or a genetic variation in *ABCB1* resulting in increased transporter activity.

The proposed mechanism suffers from a lack of evidence that many clinically used AEDs are substrates for human P-gp or any other known human blood-brain barrier efflux transporter [47]. The transporter hypothesis has also failed to receive support from recent genetic association studies, including a meta-analysis that failed to replicate early reports of an association between polymorphisms in the *ABCB1* gene and drug resistance [48].

According to the target hypothesis, epilepsy pharmacoresistance occurs when intrinsic (genetic) or acquired (disease related) changes in drug targets make them less sensitive to AEDs. Recent studies have provided evidence of reduced sensitivity to carbamazepine in brain tissue from patients who were clinically unresponsive to carbamazepine and underwent resective surgery [49]. However, it is unknown whether pharmacodynamic insensitivity in these tissues extended to AEDs with different mechanisms of action or even to other AEDs that target sodium channels. A polymorphism in the *SCN1A* gene encoding Nav1.1 sodium channels has been described, which associates with the use of higher doses of carbamazepine and phenytoin, suggesting that there is reduced sensitivity to these drugs [50]. However, this polymorphism is unlikely to influence sensitivity to AEDs that do not act through sodium channels. The acquired version of the target hypothesis proposes that the pharmacodynamic sensitivity of the AED target is modified by the disease state [51]. There are many examples of changes in the activity of voltage-gated and neurotransmitter-activated ion channels in acquired epilepsy models, some of which lead to reduced responsiveness to AEDs [52]. However, there is no evidence that the efficacy of AEDs acting on different targets is similarly affected.

An alternative mechanism for explaining refractoriness was suggested – the intrinsic disease severity [53]. This hypothesis claims that there are differences in inherent epilepsy severity reflected in the frequency of seizures in the early phase of epilepsy (the single most important factor associated with prognosis). Possibly, common neurobiological factors may underlie both epilepsy severity and drug refractoriness. These authors suggest that to advance in the understanding and therapeutic management of refractory epilepsy, it is crucial to identify biomarkers which define the most severe forms of epilepsy. Unfortunately, there are few studies on the contribution of genetics to the severity of epilepsy [53].

Treatments under Investigation

Polymers, electrical brain stimulation and prediction of seizures may be available in the future for treating patients with refractory epilepsy. Cell transplantation and gene therapy, although holding great promise, are still far from routine clinical use [54].

Polymers containing AEDs consist of 2- to 3-mm microspheres that might be placed near the epileptogenic zone. Advantages include: (1) new AEDs could be used including those which do not cross the blood-brain barrier or show systemic toxicity; (2) they may be useful when the epileptogenic zone is near eloquent cortex; (3) they prevent noncompliance [55]. Implanting wafers impregnated with chemotherapeutic agents into the resection cavity results in prolongation of survival without an increased incidence of adverse events [56]. Studies in animals have been promising as the application of polymers containing phenytoin to the epileptogenic zone in mice has reduced epileptogenic indexes [57].

Electrical brain stimulation is still not accepted as a routine treatment for epilepsy, partly because there is no

consensus regarding the better region to stimulate and in what type of seizure it is most effective. The epileptogenic zone and the centromedian or anterior nuclei of the thalamus seem to be the most effective targets for electrical stimulation [58]. The efficacy seems to be similar to vagal nerve stimulation which has a lower risk and less comorbidity [58]. This intervention is thus unlikely to be routinely used in the future.

Finally, a seizure detector coupled with a trigger AED infusion pump has been developed with success in the mouse [59]. Research has also been done in predicting seizures [60]. Hopefully, in the future a device may predict seizures and automatically administer AEDs to prevent them from occurring.

Acknowledgment

The author would like to thank José Armando Leitão for linguistic and spelling corrections.

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