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Abstract

Around 20-30% of patients with epilepsy will not fully respond to medication, with potential consequences on quality of life, morbidity and premature mortality. Early identification of drug resistance is key to offer the patient other treatments alternative, such as surgery, neuro-modulation or ketogenic diet when the disease remains disabling. Drug resistance is defined by the number of medications having failed to fully control seizures. The International League Against Epilepsy (ILAE) defines drug resistance by the failure of two adequately chosen and dosed antiepileptic drugs (AED). More generally, with an increasing number of medications tried, the less likely is the next medication to be efficacious. Several factors are associated with drug resistance: high seizure frequency before treatment and some structural brain lesions (hippocampal sclerosis, tumors, focal cortical dysplasia for instance). There is an ongoing debate if drug resistance is caused or not by a specific mechanism across different epilepsy types. Two main mechanisms are postulated; either failure of the medication to reach the seizure onset zone(s) (because of expulsion due to drug transporters) or modifications (genetic?) of the treatments' binding site. At this time, there is conflicting evidence about these hypotheses and most of these experiments need to be replicated. More generally, drug resistant epilepsy could also well relate to the severity of the underlying condition.

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Keywords: Antiepileptic drug, surgery, prognosis, determinant

Pharmaco-résistance en épilepsie

Environ 20-30% des patients souffrant d'épilepsie ne vont pas répondre complètement au traitement médicamenteux, ceci avec des conséquences potentielles sur leur qualité de vie, une morbidité accrue et une mortalité prématurée. L'identification précoce de la pharmaco-résistance est importante pour offrir un traitement alternatif efficace à ces patients tels que la chirurgie, la neuromodulation ou la diète cétogène, quand l'épilepsie reste invalidante. La résistance au traitement est définie de manière pratique par un nombre de traitements qui a échoué à contrôler complètement les crises. La ligue internationale contre l'épilepsie (ILAE) définit la résistance au traitement comme l'échec de deux traitements adéquatement choisis et dosés. Plus généralement, la chance qu'un nouveau traitement soit efficace diminue avec chaque traitement essayé sans succès auparavant. Plusieurs facteurs sont associés avec la résistance au traitement, notamment la fréquence des crises avant le traitement et certaines causes structurelles (sclérose hippocampique, tumeurs, et dysplasie corticale focale par exemples). Il y a un débat pour savoir si la résistance au traitement est lié à un mécanisme spécifique que soit le type d'épilepsie. Deux mécanismes principaux sont postulés ; un défaut d'accès du médicament à la (les) régions(s) épileptogénique(s) (en raison de son expulsion par des transporteurs) ou une modification (génétique ?) des cibles des traitements. A ce stade, il y a des preuves contradictoires à propos de ces hypothèses et la plupart de ces experimentations nécessite encore d'être répliquées. Plus généralement, la résistance pourrait aussi être le fait d'une sévérité plus importante de la cause sous-jacente.

Mots-clés : médicament antiépileptique, chirurgie, prognostic, facteurs déterminants

Pharmakoresistenz in der Epilepsie

Ca. 20-30% der Patienten mit Epilepsie sprechen nicht gut auf anfallsunterdrückende Medikation an, mit möglichen Auswirkungen auf Lebensqualität, Morbidität und Lebenserwartung. Ein frühzeitiges Erkennen der Pharmakoresistenz ist wichtig, um den Patienten alternative Therapieoptionen wie Epilepsiechirurgie, Neurostimulation oder ketogene Diät anzubieten. Pharmakoresistenz wird definiert durch die Anzahl eingesetzter Medikamente mit Persistenz der Anfälle. Die Internationale Liga gegen Epilepsie (ILAE) definiert Pharmakoresistenz als fehlende Anfallsfreiheit trotz Einsatz von zwei adäquat ausgewählten und dosierten anfallsunterdrückenden Medikamenten (AED). Prinzipiell gilt, je mehr Medikamente bereits ohne Therapieerfolg eingesetzt wurden, desto kleiner ist die Wahrscheinlichkeit einer Wirkung eines weiteren Medikamentes. Es gibt mehrere Faktoren, die mit einer Pharmakoresistenz verbunden sind: insbesondere hohe Anfallsfrequenz vor Therapiebeginn und strukturelle Hirnläsionen (z.B. Hippocampussklerose, Tumoren, fokale kortikale Dysplasie). Es bleibt umstritten, ob Pharmakoresistenz durch spezifische Mechanismen bei verschiedenen Epilepsietypen entsteht oder nicht. Zwei Hauptmechanismen wurden postuliert: Einerseits fehlende Verfügbarkeit des Medikaments in der Anfallsursprungszone (in Folge einer Elimination durch Medikamententransporter) oder durch Modifikationen (genetisch bedingt?) der Wirkstoffbindungsstelle der Substanz. Zurzeit gibt es widersprüchliche Evidenz zu diesen Hypothesen – und die meisten Versuche müssen wiederholt werden. Generell könnte die Pharmakoresistenz vom Schweregrad der zugrunde liegenden Erkrankung abhängig sein.

Schlüsselwörter: Antiepileptika, Chirurgie, Prognose, Einflussfaktor

Introduction

Epilepsy is a common neurological disease, with a lifelong prevalence 1 in 26 in the general population [1]. Between 20-30% of patients with epilepsy develop drug-resistant epilepsy [2, 3]. This figure largely reflects the hospital setting of these studies. Considering epilepsy in the general population, drug resistance could be as low as 15% [4]. Drug resistance is a major determinant of epilepsy outcome, as it is associated with a higher risk of premature death, injuries, psychosocial difficulties and poor quality of life [2].

Based on epidemiological studies [5], the International League Against Epilepsy (ILAE) has defined drug resistant epilepsy as failure of adequate trials of two tolerated and appropriately chosen antiepileptic drugs (AED) (whether as monotherapies or in combination) to achieve sustained seizure freedom [6]. This definition can be applied for a period of time and it can vary in time; a patient can be drug resistant and drug responsive at different times in the course of the disease [6]. The ILAE guidelines recommend to use "the rule of three" to define seizure control: seizure freedom is considered after three times the longest pre-intervention inter-seizure interval in the previous year or twelve months for unique seizure [7]. This "the rule of three" has been validated statistically using aleatory (stochastic) models of events. This showed that after a period of seizure freedom lasting longer than 3 times the inter-seizure interval, the likelihood of recurrence is as low as 5% [7].

The diagnosis of drug-resistant epilepsy is usually straight forward, but a few pitfalls of pseudo-resistance should be avoided. For instance, the misdiagnosis of epilepsy is a common cause of pseudo-resistance because up to 25% of patients diagnosed of drug-resistant epilepsy suffer from psychogenic non epileptic seizures [8]. In case of disabling seemingly drug resistant epilepsy, an attempt to record seizures (ideally with video EEG) should be undertaken. Another rare reason is inadequate AED choice for the type of epilepsy syndrome, as well as a suboptimal dosage of AED prescribed, leading to insufficient control of seizures [2]. Other more common possible causes include patients' lifestyle with poor treatment compliance and alcohol or drug abuse. Measuring AED plasma level after a recurrence is helpful to assess compliance. A 50% drop (or more) of plasma concentration (compared to a previous trough level) is considered as a sign of irregular medication intake [9].

Early identification of patients with drug-resistant epilepsy is important in order to offer alternative therapies, such as surgical treatments, neuromodulation therapy or ketogenic diet [2, 10]. There are evidences that earlier surgery is more likely to be successful [11, 12], although more difficult cases may also be referred later to presurgical work-up. A recent small prospective trial has indeed clearly shown the benefit of early surgery over medical management in drug resistant epilepsy [13]. This is furthermore supported by a recent European study comparing two periods of time (1997-1998 and 2012-2013), that showed that the results of epilepsy surgery tend to improve especially in MRI negative or complex cases [14].

Determinant factors of drug resistance

In two most notable studies of patients with epilepsy prospectively followed during 7 years [5] and 19 years [3], respectively, around 60% of patients were seizure free with the first or second tried AED. Several factors were associated with a poor prognosis in term of seizure control: large number of seizures before treatment (the main factor being high seizure frequency rather than the overall number) and a structural brain lesion. The nature of the lesion is also determinant in that respect [15]. Progressive lesions like tumors, hippocampal sclerosis (with continuous abnormal neuro-

genesis) and cortical development malformation (with early degenerative changes) are associated with a lower proportion of treatment responders [16]. Also, having dual pathologies (typically hippocampal sclerosis and focal cortical dysplasia) is often associated with a poor control of seizures [16].

On the other hand, a positive response to the first tried AED is understandingly a powerful prognostic factor of remission, as it has been shown in children with temporal lobe epilepsy [17]. Besides this, probability of controlling seizures decreases with each additional AED tried unsuccessfully [4, 5]. After 6 AED tried, chances to become seizure-free on medication are remote (down to a few percent) [4]. Patients with genetic generalized epilepsy usually have more chances to enter remission with AED than patients with focal structural epilepsy [5, 16, 17]. Patients diagnosed of epilepsy in adolescent or older ages seem also more likely to achieve remission with AED [2, 16, 17].

Possible mechanisms of drug-resistant epilepsy

There are different hypotheses about the cause of drug resistance in epilepsy that reflect our current lack of knowledge about the neurobiology of epilepsy. One underlying question is similar to the epilepsy mechanism in general: Is there a common additional mechanism of drug resistance that is not directly related to the pathogenesis of the epilepsy itself?

The other possibility is that there is no specific mechanism of resistance, but that pathogenesis of each epilepsy constellation can be particularly severe and lead to drug resistance; for instance, alterations in neuronal circuitry and neurotransmitter receptors seen in hippocampal sclerosis and cortical dysplasia, mutations in ion channels in some rare genetic epilepsy syndroms, or auto-immune mechanisms as in Rasmussen's encephalitis.

This debate, despite being seemingly remote from clinical practice, has potentially concrete implications. If there is indeed a specific mechanism of drug resistance, this would mean this mechanism may be amenable to a treatment.

Conversely, if drug resistance is the end result of multiple mechanisms, it is unlikely to be addressable as a whole. A fact arguing against a common mechanism is the role played by the underlying lesion in determining drug resistance. There have been, however, suggestions that a common mechanism might have a role irrespectively of the underlying cause of epilepsy [18].

Most research of a common mechanism of drug resistance has explored two aspects: Either the AED fail to reach the target because of drug transporters expelling it from the central nervous system, or the AED's cellular targets are altered, reducing the sensitivity to treatment [18, 19].

1. Drug-transporter hypothesis

AEDs need to cross the blood-brain barrier (BBB) to achieve their action in the brain parenchyma. P-glycoproteins (P-gp) are multidrug transporters located in the BBB that regulate the flow of different drugs in the brain. A gene family called MDR, with two subtypes of genes (MDR1 and MDR2) located on chromosome 7q21, expresses P-gp. Among these subtypes of genes, MDR1, also called ABCB1, expresses a multidrug-resistant transporter expressed in the brain [20].

This transporter has been well described in cancer drug resistance without establishing its exact mechanism [21], as well as in patients with HIV; its 3435 TT genotype is associated with lower nelfinavir and efivarenz plasma concentrations [22]. This drug transporter seems to regulate intraparenchymal AED concentrations in vivo in animal models [23], showing increased parenchymal carbamazepine (CBZ), phenytoin, lamotrigine concentrations once the drug transporter was inhibited [24]. P-gp expression was also shown to be increased in human epileptogenic tissues removed surgically and in post-mortem examination [25]. Increased activity of the P-gp drug transporter was also shown in vivo in patients with epilepsy using PET imaging of a transporter substrate, compared with free-seizure patients and healthy subjects [26].

There are also suggestions that P-gp genetic changes (CC-genotype compared to TT-genotype at ABCB1 C3435T polymorphism) would predispose for drug-resistant epilepsy [27]. These findings were however inconsistently replicated [28]. A more basic uncertainty about the relevance of the drug transporter hypothesis is whether AEDs are actually substrates of these transporters; experiments regarding CBZ and levetiracetam are controversial [19, 21, 29].

2. Change in AED target hypothesis

Genetic or functional modifications in the molecular drug targets can conceivably lead to a resistance to their ligands [30]. Most work in this perspective was done on sodium channels. Voltage-gated Na+ channels are formed by α and β subunits; AEDs modulating these channels mainly bind to α subunits [31]. SCN1A, SCN2A and SCN3A genes located on chromosome 2 encode several isoforms of α subunits of sodium channels. A relationship between the R19K polymorphism in SCN2A and resistance to sodium channels blocking AEDs was suggested [32].

Other changes were suggested to correlate with drug response [33]. SCN2A polymorphism IVS7-32A>G (rs2304016) was associated with resistance to sodium channels blocking AEDs, probably through splicing or gene expression as it is located in an intronic region. On the other hand, the SCN2A haplotype GCTGCGTATAAGA has been associated with a good response. On the

functional side of things, one study has shown that the carbamazepine mechanism of action – a use-dependent block of voltage-gated sodium channels – is lost in patients with a CBZ-resistant temporal lobe epilepsy in comparison with responder patients [30]. These findings were however not replicated.

To sum up, the mechanisms of drug resistance are to this day only hypotheses – most of them are still waiting to be replicated. Early identification of patients with drug resistant epilepsy remains key to improve the care of these patients.

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