

Epilepsy treatment: a paradigm shift is urgently need

Tratamento da epilepsia: uma mudança de paradigma é urgentemente necessária

Ana Paula Bartmann¹, Josemir W. Sander²

ABSTRACT

Epilepsy affects between 5 and 10 people in a 1,000 and carries considerable morbidity and premature mortality. The complex inheritance pattern of a lowered seizure threshold is not fully understood but is likely to be polygenic. In the majority of people with epilepsy, we do not understand the pathophysiology, how a seizure is triggered, and how it can be prevented. In the centennial year of the discovery of the anti-epileptic properties of phenobarbital, we have over 20 antiepileptic drugs; however, none have dramatically changed the long-term prognosis of the condition. The cascade of events triggering epilepsy is likely to vary greatly among individuals. The hope for the future is a shift of paradigm away from the symptomatic approach that currently exists. Indeed, once epileptogenesis is fully understood, treatment can be targeted at specific mechanisms, and then we will have truly disease-modifying therapies.

Key words: epilepsy, epilepsy treatment, phenotype, prognosis.

RESUMO

A epilepsia afeta entre 5 e 10 em cada 1.000 pessoas, e está associada a comorbidades e mortalidade prematura. O complexo padrão de herança, possivelmente poligênico, para baixo limiar convulsivo, ainda não é bem compreendido. Na maioria das pessoas com epilepsia ainda não entendemos a sua fisiopatologia, como as crises epiléticas são desencadeadas ou como podem ser prevenidas. No centenário da descoberta das propriedades antiepilépticas do fenobarbital, temos mais de 20 drogas disponíveis para tratamento de epilepsia; contudo, nenhum fármaco mudou dramaticamente o prognóstico desta condição, em longo prazo. A cascata de eventos que desencadeia a epilepsia, provavelmente, varia muito de indivíduo para indivíduo. A esperança para o futuro é a mudança do atual paradigma da abordagem sintomática. Uma vez que a epileptogênese seja melhor compreendida, o tratamento poderá ser direcionado aos seus mecanismos específicos e então poderemos dispor de tratamentos capazes de modificar a história natural da doença.

Palavras-Chave: epilepsia, tratamento da epilepsia, fenótipo, prognóstico.

THE CHANGING SCENARIO

Epilepsy is a syndrome-complex and not a diagnosis on itself. Many syndromes share a seizure phenotype and one syndrome may present with different seizure types. Indeed, epilepsy is the propensity to have epileptic seizures regardless of the aetiology. Many neurological conditions have the tendency to seizures as part of the phenotype.

The symptom-complex, epilepsy is responsible for approximately 20% of all neurology appointments¹. For most people with epilepsy, the first antiepileptic drug (AED) may well control seizures², and for them an issue is the likelihood

of seizures recurring if medication is withdrawn. Over 60% of people with epilepsy when treated will enter remission, but how can we identify those that are safe to take off therapy³? Questions still unanswered are: do people who enter remission as the result of the effect of the drug or is it the natural history of certain syndromes that leads to seizure freedom? The correct identification of a phenotype is fundamental for treatment and prognosis, and many new technologies are now being used to identify such phenotypes.

When prescribing AED, neurologists are aware that the likelihood of seizure remission decreases substantially with successive drugs. Indeed, if someone requires a trial of

¹MD, MSc at Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, Queen Square, London WC1N 3BG; Epilepsy Society, Chalfont Centre for Epilepsy, Chalfont St Peter, Bucks. SL9 0RJ, United Kingdom;

²MD, PhD, FRCP at Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, Queen Square, London WC1N 3BG; Epilepsy Society, Chalfont Centre for Epilepsy, Chalfont St Peter, Bucks, SL9 0RJ, United Kingdom.

Correspondence: Ley Sander; Box 29, UCL Institute of Neurology, Queen Square, London WC1N 3BG - United Kingdom; E-mail: l.sander@ucl.ac.uk

Support: The authors are based at UCLH/UCL, which receives a proportion of funding from the UK Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme. JWS is supported by the Dr Marvin Weil Epilepsy Research Fund.

Conflict of interest: There is no conflict of interest to declare.

Received 20 October 2012; Received in final form 12 December 2012; Accepted 20 December 2012.

treatment with a third or fourth AED with a different mechanism of action the success rate is still less than 10% compared with approximately 50% for the first drug⁴. This appears counter-intuitive, as it would seem rational that drugs with different modes of action would have proportionately similar rates of success. To the individual, percentages don't matter, and until now science has not provided precise answers to aid the physician choosing the right drug from the more than 20 AED available.

Around 10% of the population may have a seizure if they live to the age of 80⁵, though only around 1% of these will develop epilepsy. In clinical practice, there is a debate on when to start AED, which one to choose, the cause of epilepsy and the odds of seizure freedom. Epileptogenesis is still a poorly understood process in which the brain triggers a cascade of molecular and cellular changes after an insult, which then leads to occurrence of spontaneous seizures. The year of 2012 is the centennial of the discovery of the antiepileptic effect of phenobarbital, one of the most prescribed AED. In the interval, more than 20 new agents were released to have antiepileptic properties, and one can safely say that the effects on the brain are not fully comprehended. So far, no drug has been proven to change the course of the condition; making the term 'anti-epileptic' a misnomer, as the drugs suppress seizures, but have no effect on the underlying mechanism.

The natural course of epilepsy is not yet fully understood. In time, a significant proportion of individuals become seizure-free. It is not known if this is a long-term effect of medication or if this is indeed the natural history of the condition. Similarly to arterial hypertension, therapeutic decisions are based on the empirical knowledge of which drug has the higher rate of success and tolerable side effects. For most drugs, we know which ion channel they act upon, but a thorough understanding of the mechanism of action is still uncertain⁶. It is interesting to note that even now, we have still not found a drug with superior efficacy when compared to older drugs, such as sodium valproate as shown in the SANAD study⁷. To some extent, this is due to the fact that many of the newer drugs have similar chemical structures to existing drugs. With the exception of levetiracetam, none has been shown to be more effective, although some have a better tolerability profile. Retigabine is the one of few newer drug with a completely novel mechanism of action, by acting on potassium channels. It is approved as adjuvant therapy for resistant focal epilepsy. Having said all this, currently no AED has a clear target that will allow tailored treatment from day one. It is still very much a trial and error approach and no rational treatment is available. By the same token, currently there is little currently knowledge that will help identify people that may developed unacceptable side-effects to the existing AED.

For some people with difficult-to-control focal epilepsy and an identifiable area of epileptiform activity, surgery is an option. Selection of people for surgery is a long process, and

in the long-term, only 50% remain seizure-free 10 years after successful surgery⁸. Better prognostic evaluation is needed to predict seizure freedom.

Vagal nerve stimulation, though effective in reducing seizure frequency and for a psychotropic effect, is still not fully understood, though the mechanism may be related to nor-adrenaline release. Another surgical option currently being assessed is the use of deep brain stimulation, which has been very successful in other neurological conditions, such as Parkinson's disease and migraine⁹. Its place in the treatment of epilepsy still remains to be seen.

But all is not doom and gloom. Epigenetics has provided some insight into this matter¹⁰. In recent years, HLA allele B-1502 was found to be related to Stevens-Johnson syndrome and toxic epidermal necrolysis in the Asian population exposed to Carbamazepine¹¹, to the point where it is now practice in some countries to screen for the allele before prescribing the drug. Though we still cannot predict if a person will become seizure-free, testing the propensity to develop toxic epidermal necrolysis, the most devastating side-effect of Carbamazepine, could be lifesaving. The aim is to use this not only to identify groups more vulnerable to adverse effects of medication, but also to identify the drug of choice or even gene therapy¹².

In 2001, the discovery of a mutation on the gene SCN1A changed our understanding of Dravet Syndrome (DS)¹³. This severe refractory form of infantile epilepsy is characterised by febrile status epilepticus evolving to multiple seizure types was found to have atypical forms, and many people that had unidentified syndromes were then found to have DS. This finding made it possible to treat some individuals with stiripentol¹⁴, the only drug proven to be effective on DS in a placebo-controlled double-blind trial. In people with tuberous sclerosis, early trials suggested a reduction in seizure frequency with everolimus, a drug that has an inhibitory effect on mTOR, a protein involved in the development of tuberous sclerosis¹⁵.

Recent technological advances in neuroimaging have made it possible to identify the epileptogenic focus in otherwise normal-looking brains. Language dominance identified by functional MRI is now part of the screening of candidates for epilepsy surgery¹⁶. New imaging modalities such as optic coherence tomography (OCT) and 3D facial photography¹⁷, could identify patterns too subtle for the naked eye or funduscopy, and help to classify epilepsy phenotypes or underlying syndromes. Perhaps in the future, alongside clinical assessment, these tests will be performed to provide more precise diagnosis, prognosis and tailored treatment.

There is hope that we are witnessing an exciting moment in the history of epilepsy: the shift from an empirical to a rational paradigm of treatment, based on the full knowledge of the individual's genetic profile and on a better understanding of the mode of actions of therapeutic agents. Indeed, a conceptual breakthrough is happening with the realization

that epilepsy is always a genetic condition, in which a lower seizure threshold is part of one's genetic blueprint but not necessarily inherited. This will lead to a major improvement in the understanding and the treatment of epilepsy and will bring targeted, disease-modifying therapies to the forefront.

THE WAY AHEAD

Hughlings Jackson's definition of epilepsy as "a chronic disorder in which there are recurring, sudden, excessive and rapid discharges of the grey matter of some parts of the brain, the clinical manifestation of which are determined by the anatomical site in the brain of the discharge"¹⁸ was a major milestone in the understanding of epilepsy. Since then our understanding of epilepsy has increased exponentially. A thorough understanding of the brain, its pathologies and the effect of drugs on neurons is, however, still far from reality. In the

future, it is likely that epilepsy as a description of a disease will disappear altogether and be replaced by the realization that it is a collection of rare diseases with a common feature: the predisposition to epileptic seizures.

The greatest change in the paradigm of epilepsy treatment is yet to come: understanding the epileptogenesis, the epigenetic determinants and pharmacogenomics that will enable the development of disease-modifying therapies. Then neurologists will be able to tailor the treatment to the individual, and maybe even change prognosis rather than shooting in the dark in the hope of getting the treatment right.

ACKNOWLEDGEMENT

We are grateful to Drs Krishna Chinthapalli and Fernando Stelzer for their helpful comments on version of the manuscript.

References

1. Duncan JS, Sander JW, Sisodiya SM, Walker MA. Adult epilepsy. *Lancet* 2006;367:1087-1100.
2. Glauser T, Ben-Menachem E, Bourgeois B, et al. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia* 2006;47:1094-1120.
3. Hixson JD. Stopping antiepileptic drugs: when and why? *Curr Treat Options Neurol* 2010;12:434-442.
4. Friedman D, French JA. Clinical trials for therapeutic assessment of antiepileptic drugs in the 21st century: obstacles and solutions. *Lancet Neurol* 2012;11:827-834.
5. Neligan A, Bell GS, Shovon SD, Sander JW. Temporal trends in the mortality of people with epilepsy: a review. *Epilepsia* 2010;51:2241-2246.
6. Loeb JA. Identifying targets for preventing epilepsy using systems biology. *Neurosci Lett* 2011;497:205-212.
7. Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. *Lancet* 2007;369:1000-1015.
8. de Tisi J, Bell GS, Peacock JL, et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. *Lancet* 2011;378:1388-1395.
9. Sankar T, Tierney TS, Hamani C. Novel applications of deep brain stimulation. *Surg Neurol Int* 2012;3(Suppl 1):S26-S33.
10. Sisodiya SM, Mefford HC. Genetic contribution to common epilepsies. *Curr Opin Neurol* 2011;24:140-145.
11. Ma JD, Lee KC, Kuo GM. Clinical application of pharmacogenomics. *J Pharm Pract* 2012;25:417-427.
12. Pitkänen A. Therapeutic approaches to epileptogenesis—hope on the horizon. *Epilepsia* 2010;51(Suppl 3):S2-S17.
13. Brunklaus A, Ellis R, Reavey E, Forbes GH, Zuberu SM. Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome. *Brain* 2012;135:(Pt 8):2329-2336.
14. Chiron C, Dulac O. The pharmacologic treatment of Dravet syndrome. *Epilepsia* 2011;52(Suppl 2):72-75.
15. Franz DN, Weiss BD. Molecular therapies for tuberous sclerosis and neurofibromatosis. *Curr Neurol Neurosci Rep* 2012;12:294-301.
16. Richardson M. Current themes in neuroimaging of epilepsy: brain networks, dynamic phenomena, and clinical relevance. *Clin Neurophysiol* 2010;121:1153-1175.
17. Chinthapalli K, Bartolini E, Novy J, et al. Atypical face shape and genomic structural variants in epilepsy. *Brain* 2012;135 (Pt 10):3101-3114.
18. Hughlings-Jackson J. On the scientific and empirical investigations of epilepsies. *Med Press Circular*, 1876.