Epileptic Disord 2005; 7 (Suppl. 1): S1-S2

The modern challenges of drug resistant epilepsy

Philippe Ryvlin
Chair of the Scientific Advisory Committee of the 26th International Epilepsy Congress

Department of Functional Neurology and Epileptology,
Hospices Civils de Lyon and Université Claude Bernard Lyon 1,
Lyon, France

For many decades, the epilepsy community has addressed the burden of drug resistant epilepsy by concentrating on the development of new anti-epileptic drugs (AEDs) and more performant presurgical evaluations and epilepsy surgery procedures. This approach has resulted in some improvement, with an approximately 10% increase in the rate of seizure-free patients, in both the medically and the surgically treated populations. Nowadays, between 20% and 30% of patients with epilepsy remain refractory to all available AEDs, whereas one third of operated patients still fail epilepsy surgery.

Facing this rather unsuccessful outcome, a number of clinicians have raised new issues related to refractory epilepsy, and paved the way for a more patient's centred approach, as opposed to seizures' dedicated treatment. This ongoing research has demonstrated that our care to patients with drug resistant epilepsy could be greatly improved beyond the scope of reducing seizure frequency, providing hope both for patients and physicians stuck together in a situation of chronic treatment failure. However, other important issues remain unsolved or controversial, as for the early prediction of drug resistance, the optimal timing for considering *vagus nerve stimulation* (VNS Therapy), or the impact of epilepsy surgery on the risk of seizure related death. A better understanding of the biological mechanisms underlying pharmacoresistance represents another major challenge, which might lead to the development of "anti-drug resistance" compounds.

The 26th International Epilepsy Congress (IEC) has covered all the above issues within the largest of its seven main topics, dedicated to "Drug resistance, Epilepsy Surgery and Mortality", coordinated by Emilio Perucca. This supplement provides an overview of several of the related lectures presented during the 26th IEC.

Wolfgang Löscher first addresses the mechanisms of drug resistance, discussing both the role of an abnormal expression of multidrug transporters favoring the efflux of AEDs away from the epileptogenic tissue, and of an alteration of the voltage-gated sodium channel which represents the therapeutic target of several drugs, including carbamazepine, phenytoin, and lamotrigine (Löscher 2005, p. S3). Both mechanisms may be present from epilepsy onset, or might develop as a consequence of recurrent seizures or prolonged treatment. Recent data suggest that selective inhibitors of the major efflux transporter P-glycoprotein (Pgp) might be effective in reversing drug resistance, encouraging the development of controlled trials.

Franck Semah questions the possibility of an early prediction of pharmacoresistance, reviewing the various predictors identified so far (Semah and Ryvlin 2005, p. S10). Most of these factors reflect the presence of an epileptogenic brain lesion, among which hippocampal sclerosis and cortical dysplasia are associated with the highest risk of medical intractability, as well as the greatest chances of being successfully treated by surgery. This underlines the need of an early identification of such lesions and their associated prognosis, in order to avoid a long and deleterious delay before considering surgical treatment. Several gene polymorphisms, including that of the ABCB1 gene coding for the multidrug transporter Pgp, have been associated with refractory epilepsy, but these findings remain controversial and not yet applicable to the individual prediction of pharmacoresistance.

Emilio Perucca discusses several commonly held beliefs which might participate to a sub-optimal care of patients with refractory epilepsy (Perucca 2005, p. S14). In particular, recent data demonstrate that very few patients unresponsive to low to moderate AED doses become seizure free after increasing dosage up to the limit of tolerability. Thus, there might not be much rationale in testing every AED at the highest tolerated dose, nor to associate medications with similar mechanism of action. Conversely, drug management of refractory epilepsy might be improved in some patients by monitoring the serum levels of new generation AEDs. In any event, controlled studies are badly needed to fill the gap of knowledge in several of these areas, including the issue of drug discontinuation after successful epilepsy surgery.

Elinor Ben-Menachem and Jacqueline French argue as to whether VNS Therapy should be introduced early in the

course of drug resistant epilepsy, after the first, second or third AED failure (Ben-Menachem and French 2005, p. S22). Elinor Ben-Menachem defends this position, based on the observation that the long term efficacy of VNS Therapy appears at least comparable with that of AEDs, whereas its side effect profile evaluated since 1988 and in over 30,000 patients, seems more favourable than that of AEDs. In particular, VNS Therapy does not alter cognition, but rather improves mood and alertness. Other advantages over AEDs are better compliance and cost-effectiveness over an eight year period. Jacqueline French points to several potential drawbacks of VNS Therapy, including specific adverse events, such as cough, dyspnea, pharyngitis, voice alteration and sleep apnea. In addition, MRI of the chest, breast, or abdomen cannot be performed with the VNS Therapy System implanted, whereas the safety of a brain MRI at field strength higher than 1.5 Tesla is not guaranteed. Finally, implantation of the VNS Therapy System represents an invasive procedure which must be counter balanced by a significantly better outcome than that obtained with standard AED treatment. No controlled trial has yet addressed this important issue, but one large European study is underway to formally compare VNS Therapy to best medical treatment.

Frank Gilliam and collaborators address the vast field of epilepsy co-morbidities, pointing to the impact of depression, poor fitness, obesity, sleep disorders, and migraine, on the patients' quality of life (QOL) (Gilliam *et al.* 2005, p. S27). Mood disorders proved to represent a major contributor to QOL scores in patients with drug resistant epilepsy, and translate into a ten fold increase in suicide rate as compared to the general population. Physical fitness is diminished in the epilepsy population, due to multiple factors possibly including drug-related weight gain and a higher risk of bone fracture, and its improvement might help to reduce seizure frequency. Sleep disorders, including obstructive sleep apnea are also overrepresented in patients with epilepsy, and are likely to have a negative impact on seizure frequency and quality of life. Migraine might also complicate drug resistant epilepsy, but can benefit from AED options which have demonstrated efficacy in migraine prophylaxis, such as valproate and topiramate. All these issues stress the need for a systematic assessment of co-morbidities in the epilepsy clinic, using reliable and valid screening instruments.

Steven Schachter provides a comprehensive review of the various psychosocial dimensions which are sensitive to interventions allowing an improvement of quality of life beyond seizure control (Schachter 2005, p. S34). A number of social and interpersonal factors influence QOL regardless of seizure frequency, including social anxiety, stigma, parental anxiety and employment. Patients' and family oriented education and counselling have a significant impact on social and parental anxiety, but their influence on self reported stigma still need to be evaluated. Several psychological factors are also amenable to educational or therapeutic interventions, including seizure worry, self esteem and self-mastery. Improvement in any of these factors is likely to translate into better health outcome. Self-mastery may also improve quality of life by favouring compliance to treatment and therefore a better seizure control.

The last section of the supplement revisits the impact of epilepsy surgery on seizure related death (Ryvlin *et al.* 2005, p. S39). Seizure related death account for approximately half of the overall mortality observed in drug resistant epilepsy, the latter being five fold that of the sex and age matched population. Several temporal lobe surgery series have reported that the death rate was normal in patients free of seizures post-operatively, whereas it remained highly elevated after a failed surgery, suggesting that a successful operation might decrease the risk of seizure related death. However, other series could not replicate these findings, and failed to demonstrate a difference in mortality between medically and surgically treated cohorts of patients with drug resistant partial epilepsy. One way to reconcile these discordant findings is to consider that the subgroup of patients who will fail temporal lobe surgery already carries most the SUDEP burden pre-operatively, due to an epileptogenic network including the insula or more prone to generate secondary generalization. Conversely, patients rendered seizure free by an anterior temporal lobectomy might be at low risk of SUDEP, even before surgery. This hypothesis is currently being tested in a large ongoing study.

Obviously, the many challenges of drug resistant epilepsy are moving rapidly toward the yield of evidence based information and guidelines. We hope that this supplement and the related lectures of the 26th IEC will help to translate results from clinical research into the daily practice of all physicians involved in epilepsy care, and to eventually improve the health outcome of our patients. □

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