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Review

Epilepsy, cognition, and neuropsychiatry (Epilepsy, Brain, and Mind, part 2)

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ABSTRACT

Epilepsy is, of course, not one disease but rather a huge number of disorders that can present with seizures. In common, they all reflect brain dysfunction. Moreover, they can affect the mind and, of course, behavior. While animals too may suffer from epilepsy, as far as we know, the electrical discharges are less likely to affect the mind and behavior, which is not surprising. While the epileptic seizures themselves are episodic, the mental and behavioral changes continue, in many cases, interictally. The episodic mental and behavioral manifestations are more dramatic, while the interictal ones are easier to study with anatomical and functional studies. The following extended summaries complement those presented in Part 1.

1. Introduction

Extended summaries of presentations at the Second International Congress of Epilepsy, Brain, and Mind (Prague, Czech Republic 2012) that focused on epilepsy, cognition, and neuropsychiatry are featured in this paper. The treatment of people with epilepsy (PWE) is complicated not only because of the wide spectrum of epileptic disorders and manifestations but also because of the fact that patients very frequently suffer from comorbidities that need to be addressed. Among the latter, mental manifestations are particularly challenging. The underlying brain lesions, the ensuing electrical activity, the consequent social repercussions, among others, are important considerations when attempting to select drug therapy (or other interventions) for

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PWE. Some antiepileptic drugs (AEDs) can reduce undesired mental changes, while others can induce cognitive or mental adverse reactions. Furthermore, other drugs affecting the mind, such as antidepressants, can interact with AEDs on a pharmacodynamic level, while others may affect AED concentrations through pharmacokinetic processes. All these factors need to be considered when evaluating an individual patient and trying to optimize therapy. These issues have been reviewed and discussed comprehensively during the Second International Congress of Epilepsy, Brain, and Mind, held in Prague in 2012 and are presented in the following extended summaries.

Another topic that has emerged in the past few years is that of high-frequency electrical activity in the brain. Traditional EEG records could not record this activity, but recently, it has been realized that this activity is of importance and may be clinically helpful, for example in localizing epileptic foci. The normal and the abnormal physiology of high-frequency oscillations are still being investigated, and several of the new developments are reviewed in this section as well.

People with epilepsy may have difficulties in social integration. Traditionally, this has been ascribed to discrimination. However, recent research has suggested the possibility of an additional contributing factor. Thus, it is possible that patients' behavior may contribute. In that respect, an interesting emerging issue deals with emotion recognition (and expression) by an individual and its possible effects on social cognition and reactions. Data, reviewed here, suggest that PWE may have particular difficulties in that respect.

Neuroimaging of mental states is another attractive and vibrant field of research. The availability of fMRI to examine brain activity during induced or spontaneous "state of mind" is a topic of recent investigations in neurology, psychiatry, and psychology. A relevant question is whether the manifestations observed in PWE are similar or different (qualitatively or quantitatively) from those occurring in others. Another relevant question, discussed here, is to what extent psychic states (such as depression) have the same anatomical correlates in PWE and in people without epilepsy.

2. AEDs and cognition, emotion, and behavior

2.1. AEDs, cognition, and behavior

Marco Mula

Antiepileptic drugs (AEDs) continue to be the mainstay of epilepsy treatment, but benefits of seizure control need to be weighed carefully against possible adverse effects, which can include behavioral problems and psychiatric disorders. In fact, AEDs have a number of mechanisms of action that are likely to be responsible not only for their antiseizure activity but also for their effects on mood and behavior.

A number of studies suggest that treatment with some AEDs may be associated with the occurrence of depressive symptoms, while other AEDs are probably antidepressants. In general terms, the links between depression and barbiturates [1], vigabatrin [2], tiagabine [3], and topiramate [4] seem to be firmly established. In the majority of cases, rapid dose titration in patients with drug-refractory epilepsy [5], a past history of depression [6], and limbic system dysfunction represent major determinants. In fact, it has been pointed out that a subgroup of patients with drug-refractory temporal lobe epilepsy seems to be particularly vulnerable to the psychotropic effects of AEDs independently of their specific mechanisms of action [6].

Psychoses related to AEDs are usually due to AED toxicity or occur in the context of the so-called forced normalization phenomenon. This concept refers to the publications of Heinrich Landolt, who reported a group of patients with florid psychotic episodes associated with "forced normalization" of the EEG [7]. Subsequently, Tellenbach [8] introduced the term "alternative psychosis" for the clinical phenomenon of the reciprocal relationship between abnormal mental states and seizures, which did not, as Landolt's term did, rely on EEG findings. Since the early observations of Landolt, a sufficient number of patients with alternative psychosis have been reported [9]. The clinical presentation does not necessarily need to be a psychosis, but this is probably the most common. The disturbed behavior may last days or weeks and is often self-limiting with the reappearance of seizures. Landolt originally associated this phenomenon with focal epilepsies, but subsequent studies suggested an association with generalized epilepsies. In any case, what seems to be striking is the association with neurobiological mechanisms underlying seizure control. In fact, forced normalization has been reported not only with AEDs but also with vagus nerve stimulation [10] and may probably be implicated in psychoses following epilepsy surgery.

On the other hand, it is important to acknowledge that AEDs are extensively used in psychiatric practice for a broad spectrum of psychiatric disorders. The primary application is in mood stabilization [11], but interesting data are also emerging regarding anxiety disorders [12] and withdrawal syndromes [13].

As for the old generation of AEDs, both carbamazepine and valproate demonstrated positive psychotropic properties upon their introduction for the treatment of epilepsy [14]. Over time, a number of controlled studies have been carried out in patients with acute mania evaluating the effects of these two AEDs against placebo, lithium, or antipsychotic drugs and demonstrating positive effects, especially in subjects with unstable forms of bipolar disorder such as those who rapidly cycle [15]. As far as new compounds are concerned, some (i.e., tiagabine and gabapentin) have failed to show any efficacy in primary psychiatric disorders, while others (e.g., topiramate) might have adjunctive uses, such as the management of weight gain associated with atypical antipsychotics or in the treatment of eating disorders [16]. Data about oxcarbazepine are definitely less conclusive than those regarding carbamazepine. Oxcarbazepine seems to be as effective as carbamazepine in acute mania but is better tolerated [17]. Cumulative results of the studies on lamotrigine provide evidence that it is effective in the management of the depressed phase of bipolar disorder type II and in the long-term maintenance treatment of patients with rapid cycling bipolar disorders [15].

Some new generation compounds (i.e., gabapentin and pregabalin) have demonstrated some efficacy in anxiety disorders [12]. For both drugs, N–P/Q type channels represent the main molecular target, in particular the alpha-2-delta subunit, type 1 and type 2. Pregabalin is probably the most interesting molecule in this regard, with a number of controlled studies demonstrating that it is better than placebo in generalized anxiety disorder [18].

Considering the number of AEDs available for the treatment of epilepsy, tailored treatment strategies that take into account comorbidities (i.e., psychiatric and cognitive problems) and the patient's needs are warranted.

2.2. Epilepsy, antiepileptic drugs, and emotions

Andres M. Kanner

One out of every three people with epilepsy (PWE) is likely to experience mood and/or anxiety symptoms over their lifetime that can present as defined disorders, according to predetermined diagnostic criteria, or as clusters of symptoms [19]. The cause of these "emotional disturbances" is multifactorial, including a family and a personal psychiatric history preceding and/or following the onset of epilepsy, neurochemical and structural changes associated with the seizure disorder, type of epilepsy syndrome, psychosocial obstacles, and iatrogenic effects. Indeed, antiepileptic drugs (AEDs) can play a significant role in the "emotional profile" of PWE through their effects on seizure control and the positive psychotropic properties of some drugs impacting mood and/or anxiety disorders. For example, in the treatment of primary mood disorders, AEDs with mood stabilizing properties that have shown efficacy in double-blind placebo-controlled trials