임 성 철
가톨릭의대

Epilepsy

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This lecture reviews the recent advances in therapeutics and underlying mechanisms of epilepsy. In particular, we review the data on the type of epilepsy, the action mechanism of antiepileptic drug(AEDs), and the choice of AEDs. Finally, the recent trends of research, which is shifting from seizure control to prevention of epiletogenesis, is discussed on this lecture.

Key Words: Epilepsy, Antiepileptic drug, Epileptogenesis, Update

Classification

The definition of epilepsy has always been a problem.[1] Previous classifications attempted to reconcile these difficulties by explaining different electroclinical syndromes, but should incorporate new data from modern imaging and genetics. The International League Against Epilepsy(ILAE) has attempted to synthesize the recently agreed views.[2] The results recognize that the syndrome is multifaceted and promise to be useful and practical.

Antiepileptic drugs and underlying mechanisms

In 2000, Kwan and Brodie[3] found that 63% of epilepsy patients were seizure-free with medication. It has been found that, despite developments of numerous new AEDs since then, the proportion of patients who did not have seizures by drug treatment remained unchanged in 2017.[4] The action mechanism of AEDs affecting ion channels or neurotransmitters remains unchanged, but the evidence of differential effects in certain syndromes is gradually increasing. Not all patients respond equally to medication. EEG studies, comparing patients who responded to valproate and those who were resistant, suggested that EEG patterns could predict the differences in drug response.[5] Genetic understanding has influenced pharmacological treatment. It has been found that sodium channel blockers can be harmful to children with Dravet syndrome.[6]

Cannabis contains approximately 80 different active cannabinoids and was used in the nineteenth century as an AED. It has been known for many years to be an antagonist at NMDA receptors with antiepileptic activity. Clinical studies in the 1970s and 80s reviewed in pointed to antiepileptic effects and recent anecdotal evidence and an open labelled trial have shown benefit in epileptic encephalopathies such as Dravet syndrome. Although

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their mechanisms point to a potential role for cannabinoids of relevance to epilepsy, there are as yet, no good studies to support their widespread use. Cannabinoids should be avoided by those with epilepsy, especially the young, who are already at risk of psychiatric problems, until good quality trials support their use.

Genetics

Despite strong epidemiologic evidence for the genetic basis of IGE, finding relevant genes remains difficult. A recent genome-wide linkage study suggested a link to the SCN1A of protocaderin PCDH7 and PCDH19, both of which are known to be associated with epilepsy and learning disabilities.[7] Analysis of microdeletions in generalized epilepsy revealed an increased burden (7.3%) compared to controls (4%) and relevance to specific genes of various genes known to be important for epilepsy, psychiatric and neurological development.[7] Mutations in the SCN8A gene are associated with epilepsy and sometimes with Dravet-like syndrome. However, However, the phenotype may depend on the pathophysiology of the mutation.[8]

Epileptogenesis

Another focus is the mechanisms of epileptogenesis; the process from initiation of pathological changes to the development of epilepsy and possibly the maintenance of epilepsy. There are changes, which involve altered gene expression, inflammation, protein production and changes in connectivity, which may all be the target for drugs to suppress epileptogenesis. One of the most studied pathways links to the rapamycin (mTOR) pathway. Upregulation of mTOR, a serine/threonine protein kinase, occurs as a result of the TSC1 and TSC2 mutations of tuberous sclerosis (TS) complex.[9] The recent double-blind study of 366 patients showed a dose-related seizure reduction of up to 40% with everolimus, in patients with TS.[10]

Whilst immunological mechanisms are clearly implicated in the etiology of certain epilepsies such as limbic encephalitis or Rasmussen encephalitis, increasing attention has been given to them in commoner forms of epilepsy.[11] There is broad evidence for their significance, especially from animal studies and involving cytokines, changes in the blood brain barrier and pathological alterations associated with altered excitability. These interact through interleukin IL1-b. A recent study of patients with moderate to severe cerebral trauma found a relationship between cerebrospinal fluid IL1-b levels and an allelic variant of the IL1-b gene to the risk of developing epilepsy.[12] This provides the first evidence of a biomarker that might be used to predict epilepsy after an epileptogenic insult and possibly a means of pharmacological intervention.

Epilepsy surgery

Given the low chance of response to medical therapy after the failure of two AED,[13] this is the widely accepted yardstick for defining refractoriness and the appropriateness for consideration of resective epilepsy surgery. The mortality of surgery is around 0.1–0.5%,[14] similar to the annual rate of SUDEP in refractory epilepsy.[15] The treatment is cost-effective in the long term, with sustained remission and close to half of adult patients and 86% of children may be able to stop their AEDs. The recent studies have found risk factors for seizure recurrence after post-operative drug withdrawal included pre-operative seizure frequency and post-operative EEG abnormalities.[16] Negative prognostic factors include high seizure frequency and long duration at baseline.[17]

Advances in epilepsy surgery include alternative methods to resective surgery; improvements in techniques of case selection for surgery and neurostimulation techniques. The identification of patients who will benefit from epilepsy surgery relies on the demonstration of a single brain region responsible for the epilepsy, which can be safely resectable. Identification of a responsible lesion has been demonstrated in numerous studies to predict a better outcome.[18]

Where resective surgery is not possible, palliative stimulation techniques may be considered. An analysis from the vagus nerve stimulation(VNS) registry combined with pooled study data totaling 8423 patients[19] found that responder rate, defined by a 50% seizure reduction, was 47% at 0–14 months and 63% at 24–48 months with seizure free rates rising from 5–10% over the same period. Responsive neurostimulation(RNS) involves a closed circuit of intracranial electrodes with electrical stimuli delivered to the brain according to a seizure detection paradigm. The circuit is often installed following electrode placement in an unsuccessful attempt to identify a surgical target. In 191 patients there was a 37.9% responder rate compared to 17.3% in the sham group.[20] Electrodes placed in the thalamus have been associated with a 69% median reduction in seizure frequency and a 35% rate of serious adverse events, including infection in 10% and lead misplacement in 8%.[21]

Conclusion

The recent epilepsy research has started to change our thinking and approach to patients, as we slowly move towards a more rational basis by which to treat this common condition.

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