

## Recent Advances in Epilepsy

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### Abstract

Epilepsy is an ancient disease which poses questions to neuroscience. It is an important disease which is updated continuously. A brief overview of the recent advances in certain controversial aspects such as epilepsy associated comorbidities like intellectual disability, multiple sclerosis, Indian epidemiology, epilepsy etiopathogenesis, genetics, PNES, seizure prediction, epilepsy surgery, AEDs and paediatric epilepsy are summarised in this review.

**Keywords:** *Epilepsy; Intellectual Disability; Multiple Sclerosis*

### Introduction

Epilepsy is a disease like a spider. It has a web that has its nemata into every aspect of human existence. Mythology describes it as exorcism and poltergeist phenomenon. Sociology recognises it a stigma as poisonous as arsenic. Neurology accepts it a challenge as frustrating as holding water in a sieve. On every front the disorder poses challenges and this fact is reflected in the innumerable controversies that cloud over seizure disorders. If a subject is inviting such rigorous scientific debate, it is proof that the issue is alive and thriving and that the best in the business are engaged in untangling the knots in the problem. This translates into ever improving definitions and fine tuning of our knowledge of the subject. And this process of change shimmers like desert heat in the form of many doubts, questions and debates. It therefore incumbent on the physicians to be very cautious in dealing with a case of epilepsy and to be updated about the disease at every possible opportunity.

### Epidemiology

As a disease of antiquity, there have been numerous studies that describe the characteristics of the disorder. In recent years there have been certain new associations that have come to the fore.

### Epilepsy and intellectual ability

It has been found that 14 - 24% of the intellectually disabled population are affected by epilepsy [1,2]. The prevalence of epilepsy also increases with the severity of the disability, 7% in people with mild to moderate disability, 67% in people with severe [3], and 50 - 82% in people with profound disability [4,5]. The association has been found to be valid both ways [6,7]. A linear decline in IQ is also seen among people who developed epilepsy [8]. Studies have shown correlation of epilepsy with poor cognitive function [9,10]. Likelihood of suffering from epilepsy increases as IQ scores drop [11], and many studies clearly show that epileptics tend to suffer psychiatric disorders [48].

### Multiple sclerosis and epilepsy

Large population-based studies confirm that there is elevation of risk of epilepsy after MS was 3- to 4-fold. It was highest in the young-

est age groups [12], frequency of seizures correlates with the number of flare-ups of MS [13], epileptic brains with MS show more severe cortical inflammation, and a higher number of intracortical lesions, than those with MS alone [14,15]. Dr Waxman of Yale School of medicine hypothesizes that the abnormal sodium channel expression found in the neurons of some patients with MS initiates development of MS and precipitates the subsequent occurrence of epilepsy [16].

### Other Comorbidities

CDC analysis of epileptics in the U.S. population [17] found that cardiovascular and metabolic disorders were common among adults with epilepsy. The prevalence of heart disease was higher among adults with epilepsy (18.3%), than among those without epilepsy (11.3%), higher blood pressure (34.2%) than those without epilepsy (29.0%), had experienced a stroke more than in adults without epilepsy (2.4%), had prediabetes than adults without epilepsy (4.3%) and tended to suffer with obesity (34.1% vs. 27.5%).

Adults with epilepsy had more prevalence of emphysema, chronic bronchitis and asthmatic attacks than those without the disorder. epileptics suffered with inflammatory disorders like dermatitis and arthritis. Even cancer was more common in adults with epilepsy (11.3%). This data highlights the wretched health conditions epileptic patients endure.

On a more unorthodox note research has also been done to test the validity and reliability of characterizing epilepsy based on an external review of medical records. Thank fully the method has proved that the method of medical record review is good enough for collecting valid research data [18].

### In India

Multiple epilepsy prevalence studies carried out in India with a report a range from 2.5 to 11.9 per 1000 population. A meta-analysis of 26 of these studies reveals a considerable heterogeneity in etiology [19]. Neurocysticercosis and febrile seizures are probably the commonest underlying causes in India [20].

- Most incidence study suggests an age standardized incidence rate of 27.3/100,000 per year [21].
- In one South Indian study show that 10% of patients with altered mental status have non convulsive status epilepticus [22]. Studies from Lucknow, Hyderabad, and Mumbai have confirm that the incidence and mortality rates of status epileptics are higher in India, due to a higher proportion of central nervous system (CNS) infections, delay in onset to hospitalization, and lack of diagnostic and treatment facilities [23-25].

### Research needs and Problem statement in India

- Adequately designed population-based case control studies of epilepsy in India which focus on the usual risk factors and use imaging and serology for infections such as cysticercosis, are necessary in order to design a suitable prevention program.
- It will be necessary to know the odds ratio of various risk factors for epilepsy and the attributable risk of these factors.
- There are no population-based studies on status epilepticus (SE) in India.
- Nonconvulsive status epilepticus (NCSE) is usually not identified as it requires electroencephalography (EEG) facilities in the intensive care unit (ICU) for diagnosis.
- Studies to understand relapses and remissions are also needed.
- The magnitude of epilepsy treatment gap in India ranges from 22% (urban middle income) to 90% (villages) [26]. Therefore health care professionals should adopt districts and engage with primary health centre staff and state government health officials to identify patients with epilepsy and treat them.

Various studies show that majority contact a health-care provider for their first episode. The most common first link of care for the patients is a secondary level government hospital. The next common is private practitioners, followed by tertiary care hospitals, and registered medical practitioners. Not surprisingly, henceforth traditional or faith healers were regularly consulted at some point of time for cure [35].

### Itiopathogenesis

The fundamental process that occurs for a seizure is repetitive transmission impulses from one part of the brain to the other in a sudden outburst. It is known that the impulse transmission is a function of the cell membrane. This transmission occurs along the cell and in between cells. The cells can be neurons or it's supporting cellular components. Any disturbance in the normal physioanatomy of this network can produce seizures.

### DNA of Epilepsy

Newer insights into the disorder are being updated making our knowledge more and more accurate.

- Shinohara, *et al.* have showed that AA diplotype of ADORA2A is associated with Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) by altering the intracellular adenosine/cAMP cascade, thereby promoting seizures and excitotoxic brain damage in patients [32].
- In patients carrying loss-of function mutations in KCNQ2, retigabine might correct the loss of function in the potassium channel and in doing so reduce or eliminate seizures.
- Autoimmunity against neuronal epitopes as a precipitating cause of epilepsy is now being studied [49,50].
- Treatment directed towards extracellular autoimmune targets such as NMDA receptors respond well to treatment in 75 - 90% of patients [51].

### PNES

Psychogenic non-epileptic seizures (PNES) affect between 12% and 20% of patients in epilepsy clinics [36]. The International League against Epilepsy provided a set of guidelines for the treatment of PNES [37].

- (1) Adequate communication and education particularly at the time of initial diagnosis,
- (2) Continued neurological follow-up to safely withdraw anticonvulsant medications and
- (3) Combined management with psychiatry to address co morbid psychiatric diagnoses.

These events represent a subconscious dissociative physical response to distressing internal emotional stimuli [38]. We know that as in depression and stress response, PNES is associated with decreased serum levels of brain derived neurotrophic factor (BDNF) and increased diurnal cortisol levels [39-41]. There are no genetic or post-mortem investigations have been conducted in patients with this disorder. It is associated with cortical thinning in the right motor and premotor regions as well-bilateral cerebellar. [42]. Preliminary functional MRI studies have identified abnormally strong functional connectivity between the insula and frontal regions involved in the executive control of motor action [44]. Working models of PNES and other dissociative motor symptoms propose that emotional triggers can bypass the normal executive control of motor behaviour through pathologically strengthened functional connections between emotional centers and motor regions [45].

### Vagal nerve stimulation

VNS may be considered for seizures in children, for LGS-associated seizures, and for improving mood in adults with epilepsy [34].

### Seizure prediction

Seizure diary has been considered the gold standard for seizure prediction, but Cook, *et al.* study states that this underestimates the frequency of occurrence and it showed the usefulness of intracranial electroencephalographic monitoring in ambulatory patients with drug-resistant epilepsy [29].

### Epilepsy Surgery

The common resective procedures in children are Focal resections involving the temporal and frontal lobes, with cortical malformations the most common underlying pathology. Hemispherectomy or multilobar procedures are more commonly performed in children younger than four years. Seizure free rates reach 60-80% [47].

Mesial temporal lobe surgery is able to keep patients seizure free for two decades. Removal of the neocortex does not lead to better seizure control [28]. Temporal lobe resections within the language dominant hemisphere can be accompanied by a decline in verbal memory performance [30].

Research [32] shows that presurgical intelligence is an indicator of the functional integrity of the contra lateral hemisphere, which mainly determines postsurgical cognition and psychosocial outcome. Seizure freedom promotes cognitive improvement.

### And paediatric epilepsy

Factors influencing paediatric epilepsy care included the child's impairments and seizure presentation, parents and the community system. Barriers identified were, limited levels of evidence about diagnosis and management, limited access to epilepsy specialty care and behavioural health care [33].

The science of epilepsy has come a long way but is still riddled with many questions that will keep neuroscientists and clinicians interested in the elucidation of this age old enigma.

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