Recent advances in Epilepsy Research in India

Aparna B Dixit¹, Jyotirmoy Banerjee¹, P Sarat Chandra², Manjari Tripathi³

Abstract:
There are more than 10 million persons with epilepsy (PWE) in India. Despite availability of antiepileptic drugs (AEDs), there is a large treatment gap varying from 50 to 70% among PWE. For treatable epilepsy, this gap can be attributed to poor education, poverty, cultural beliefs, stigma, and poor healthcare infrastructure; whereas for chronic epilepsy, this gap can be attributed to lack of proper diagnosis and treatment. To prevent, treat, and cure epilepsy, researchers worldwide have made exciting advances across all areas of epilepsy research. Studies carried out in India have also shown substantial progress; however, most of them are focused on the epidemiological aspects of epilepsy, genetic associations, identification, and validation of new AEDs in animal models of epilepsy. Very few studies are reported on understanding the process of epileptogenesis, a dynamic process by which neurons begin to display abnormal firing patterns that cause epileptic seizures. Animal epilepsy models can be used for in depth studies; however, studies conducted on resected brain tissues from epilepsy patients are clinically relevant. Finally, more funding support from government and collaborations among basic research institutes, medical institutes, as well as industries is required to raise the standards of epilepsy research in India. This review focuses on the evaluation of the current status of epilepsy research in India and the need to identify potential anti-epileptogenic interventions.

Key Words:
Antiepileptic drugs, biomarkers, epilepsy, epileptogenesis

Key Messages:
In India, substantial progress has been made on the epidemiological aspects of epilepsy, genetic associations, identification, and validation of new antiepileptic drugs; however, research focusing on understanding of the process of epileptogenesis to identify new drug targets is still in its infancy and demands more attention.

Epilepsy is one of the most common neurological diseases causing significant medical and social morbidity. Epilepsy is characterized by recurrent, usually unprovoked, epileptic seizures, as well as by the cognitive, psychosocial, and social consequences of this condition.¹² The disturbances of neuronal activity that occur during seizures may result in strange sensations, emotions, and behaviors. They may also sometimes cause convulsions, abnormal movements, and loss of consciousness.³ There are 50 million people living with epilepsy worldwide, and most of them reside in developing countries. It is estimated that there are more than 10 million persons with epilepsy (PWE) in India. Its prevalence is approximately 1% of our population and is higher in the rural (1.9%) compared with the urban population (0.6%). The burden of epilepsy, as estimated using the disability-adjusted life years (DALYs), accounts for 1% of the total burden of disease in the world. This does not take into account the morbidity caused by social stigma and isolation, which PWE in our country face; this in turn leads to escalation of the disease burden.⁴ The disorders affect both male and female subjects and can develop at any age. Despite advances in epilepsy treatment, a large treatment gap exists in India, which can be attributed to the lack of knowledge of antiepileptic drugs (AEDs), poverty, cultural beliefs, stigma, poor health care infrastructure, and shortage of trained professionals. The annual economic burden of epilepsy in India is 88.2% of the gross national product (GNP) per capita and 0.5% of the GNP.⁵

On the basis of etiology, epilepsy can be divided into three major categories: Idiopathic, symptomatic, and cryptogenic. Idiopathic epilepsies are generally thought to arise from...
Another study synthesized the potential epileptogenic insult leads to prolonged status epilepticus. We identified the association of genetic abnormalities; symptomatic epilepsies arise from the effects of an epileptic lesion, which could be focal, such as a tumor, or a defect in metabolism; cryptogenic epilepsies involve a presumptive lesion that is difficult to uncover during evaluation.[20] The symptoms vary considerably from one person to another. In some cases, people experience a type of seizure complex called status epilepticus. These are defined as seizures that last for more than 5 minutes or seizures that recur without recovery of consciousness. Prolonged status epilepticus can damage the brain and may be life-threatening.[23] Infectious diseases play an important role in the development of seizures and on the long-term burden causing both new-onset epilepsy and status epilepticus. It is estimated that nearly 2–3 lakh patients may die due to epilepsy if they remain untreated.[21]

Despite the availability of a range of AEDs, approximately three-quarters of the individuals diagnosed with epilepsy continue to experience seizures; such epilepsy is referred to as pharmacoresistant epilepsy (PRE). A small proportion of the PRE patients undergo therapeutic resection of the epileptogenic zone (EZ). Accurate localization of the EZ is an important issue in epilepsy surgery because EZ is not discrete and focal, rather the epileptogenic networks can spread ictal activity to different regions of the brain. To decipher the molecular-clinical mechanisms underlying epilepsy, including PRE, it is necessary to understand the dynamic process of epileptogenesis.[8] Brain insults such as traumatic brain injury (TBI), ischemic stroke, intracerebral hemorrhage, infections, tumors, cortical dysplasia, several neurodegenerative diseases, and prolonged acute symptomatic seizures such as complex febrile seizures or status epilepticus[10] can induce “epileptogenesis,” a process by which normal brain tissue is transformed into tissue capable of generating spontaneous recurrent seizures. Epileptogenesis is a dynamic process and can recruit distantly connected areas in a cascade of spreading activity from the central epileptogenic focus outward through both normal and abnormal brain tissues to different parts of the brain.[11] Thus, the process of epileptogenesis itself may lead to the development of pharmacoresistant epilepsy. Numerous reports on epileptogenic process have been published in recent years to understand the different stages involved in the process. A study reported that a potential epileptogenic insult leads to prolonged high rates of nonlinear dynamical regimes of intermittency type as the hallmark of epileptogenesis.[12] Another study reported that antiepileptogenic repair of excitatory and inhibitory synaptic connectivity after neocortical trauma.[13] Studies show the common mechanisms underlying epileptogenesis and the comorbidities of epilepsy.[14] Several studies at molecular level have identified antiepileptogenic targets. mTOR pathway inhibition has been proposed as a new therapeutic strategy in epilepsy and epileptogenesis.[15] Regulation of the cell surface expression of chloride transporters have been associated with epileptogenesis.[16] Synaptic vesicle glycoprotein 2A (SV2A) have been shown to regulate kindling epileptogenesis via GABAergic neurotransmission.[17] Recently, LAU-0901 was identified as an antiepileptic drug which antagonises platelet-activating factor receptor (PAF-r), mitigating dysfunctional epileptic neuronal circuits and dysmorphic dendritic spines.[18] Many groups are focusing on the development of better model systems to understand the process of epileptogenesis. A refined model of acquired epilepsy for the identification and validation of biomarkers of epileptogenesis have been developed in rats.[19] A recent study used multimodality imaging to assess the blood–brain barrier impairment during epileptogenesis.[20] Early recognition and intervention in the epileptogenic process could prevent the development of chronic epilepsy/PRE in patients with epileptic seizures. Many studies in various aspects of epilepsy including PRE have been reported from different parts of India; however, most of them have examined the association of genetic variants, efficacy of already existing AEDs, or identification of new AEDs. Very few studies have focussed on understanding the process of epileptogenesis, identifying the patients at risk for chronic epilepsy, and finding new treatment options to prevent chronic epilepsy in these patients. In this review, we have provided an overview of the recent advances in different areas of epilepsy research in India. We have also proposed that more studies should be conducted on the valuable human brain tissues to identify new drug targets with antiepileptic or disease modifying effects.

**Research Progress in Epilepsy**

Indian Epilepsy Association (IEA) affiliated to International Bureau of Epilepsy (IBE), and Indian Epilepsy Society (IES) affiliated to International League Against Epilepsy (ILAE), are the two major epilepsy societies in India. IEA and IES consist of medical doctors and professionals from the fields of epilepsy. The role of IEA and IES is to form a task force to liaise with traffic authorities, public health officials, epidemiologists, and importantly, sister organizations, such as the Indian Academy of Paediatrics and Indian Medical Association, with the aim of preventing epilepsy. There are four medical institutes in India, All India Institute of Medical Sciences (AIIMS), New Delhi, National Institute of Mental Health and neurosciences (NIMHANS), Bengaluru, Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTMIST), Thiruvananthapuram, and Christian Medical College (CMC), Vellore, that are extensively involved in clinical as well as basic epilepsy research.

**Research progress in the causes of epilepsy**

Several studies have reported the existence of various forms of epilepsy associated with different causes in India, including symptomatic epilepsy, idiopathic epilepsy, partial generalized seizures, and the unclassified type of epilepsy.[21] Many case control studies in India have found febrile seizures, head injury, developmental delay, as well as family history of epilepsy, birth by complicated delivery, and neonatal seizures to be significant risk factors.[21]

**Role of infections**

The central nervous system (CNS) infections are a major cause for acute symptomatic epilepsy. Seizures are not uncommon in patients with human immunodeficiency virus (HIV) infection, tuberculous meningitis, rabies, Japanese B encephalitis, and malaria. Neurocysticercosis (NCC) is the most severe form of cysticercosis in which cysts develop in the CNS. Most of the recent research is focused on NCC-associated epilepsy. It was estimated that in 2011, human NCC-associated active epilepsy caused an annual median loss of Rupees 12.03 billion with losses of Rupees 9.78 billion from north India and Rupees 2.22 billion from south India. The results indicate that human NCC causes significant health and economic impact in India.[22]
Role of genetic variants

Large number of studies published in recent years in India have focussed on the identification of the association of genetic variants with epilepsy. Past research work has shown an association of hot water epilepsy (HWE) with family history, and two loci for HWE at chromosomes 1q21.3-q22.3 and 4q24-q28 were identified. Exome sequencing suggested EATT3 or SLC1A1 gene, a glutamate transporter gene, as the causative gene. Studies have shown association of KCNQ3 and hSKCa3 genes, absence of GABRA1 Ala 322Asp mutation, association of KCNQ3 gene in juvenile myoclonic epilepsy and polymorphisms in BRD2, and LGI4 as risk factors for juvenile myoclonic epilepsy. Reelin (RELN), located on human chromosome 7q22, is considered to be a potential candidate gene for childhood epilepsy. In a study conducted in West Bengal, India, 63 patients with childhood-onset epilepsy and 103 healthy controls were recruited. Case-control analysis revealed significant over-representation of G/C and G/C/C/C genotypes, and C allele of exon 22 G/C marker (rs362691) in cases compared to controls. Recently toll-like receptor-4 polymorphisms and serum matrix metalloproteinase-9 were identified in newly diagnosed patients with calcified NCC and seizures.

In our recent report, we did not find mutations in GABRG2 receptor gene as a major factor in the pathogenesis of mesial temporal lobe epilepsy (TLE) in the Indian population. Samanta et al., reported epilepsy with PCDH19 mutation that was masquerading as benign partial epilepsy in infancy. A recent study shows the genetic association of KCNJ10 rs1130183 with epilepsy; and, the computational analysis of the deleterious nonsynonymous single nucleotide polymorphisms (SNPs) of KCNJ10 gene also showed association with seizure susceptibility.

Another study revealed that pyridoxine-dependent epilepsy is associated with antiquitin deficiency mutation in the ALDH7A1 gene. Srikumar et al., explored the structural insights on human laforin mutation K87A in Lafora disease, and identified that the flexibility of K87A mutated laforin structure, with replacement of acidic amino acid to aliphatic amino acid in the functional carbohydrate binding module (CBM) domain, have more impact in abolishing glycogen binding that favors Lafora disease. Dubey et al., identified and characterized novel splice variants of the human EPM2A gene mutated in Lafora progressive myoclonus epilepsy. They identified three novel EPM2A splice variants with the potential to code for five distinct proteins in alternate reading frames and suggested that alternative splicing could possibly be one of the mechanisms by which EPM2A may regulate the cellular functions of the proteins it codes for. Ring chromosome 20 [r(20)] manifests as a refractory epilepsy syndrome with complex partial seizures (CPS), nocturnal frontal lobe seizures, and nonconvulsive status epilepticus (NCSE) in a majority of cases.

Research progress in the diagnosis of epilepsy

The diagnosis and management of PWE are based on the accurate historical description of the ictal event. An accurate description helps in correctly classifying the seizure type and epilepsy syndrome. It also guides the physician in starting the appropriate AED for the PWE. In patients with drug-resistant epilepsy, the description of semiology also helps in the localization and localization of the possible ictal onset zone. The gold standard for determining semiology is the video electroencephalogram (EEG) recording, and several studies have focused on the accuracy of investigations such as EEG, ictal single-photon emission positron computed tomography (SPECT), and positron emission tomography (PET). We recently systematically evaluated the accuracy of home videos in assessing the semiological signs in PWE. India has the second largest percentage of mobile phone users, and this valuable tool had never before been evaluated for assessing PWE (http://en.wikipedia.org/wiki/Listofcountriesbynumberofmobilephoneusers). The results of our study show that the widespread availability of mobile phones, even in the rural areas of the country, can be harnessed to capture seizures and classify epilepsy accurately. This will have long-term implications for patient management as well as for clinical research of PWE in India. In one of our cross-sectional studies, we have assessed the impact of clinical epilepsy severity and pretreatment hypsarrhythmia severity on epilepsy and cognitive outcomes in treated children with West syndrome. We have reported that the Kramer Global Score ≤8 and Early Childhood Epilepsy Severity Score (E-Chess) ≤9 in the past 1 year were associated with a favourable epilepsy outcome but not with the neurodevelopmental or motor outcome.
Recently Mahale et al., reported that predictive factors for acute seizures are altered mental status (GCS < 8), focal deficits, hemorrhagic infarct, involvement of frontal lobe, and superior sagittal sinus with high D-dimer levels. Datta et al., performed multiparametric magnetic resonance imaging (MRI) studies of hippocampus and amygdalae in temporal lobe epilepsy (TLE) and suggested that readily measurable single-slice parameters (Hippocampal angle [HA], parahippocampal angle [PHA] and medial distance ratio [MDR]) can readily delineate TLE in a time-constrained clinical setting, which contrasts with customary three-dimensional hippocampal volumetry that requires many slice computation. We have published a screening tool to identify surgical candidates with drug refractory epilepsy in resource-limited settings. Using the best available evidence, we have developed a decision-making tool which can provide a comprehensive quick guide for determining candidacy for epilepsy surgery evaluations in resource-limited settings.

Research Progress in the Treatment of Epilepsy

New drug treatment

Synthetic drugs

Ongoing basic research efforts throughout the world, including India, continue to identify targets for therapy development. Most studies focus on the role of either gamma-aminobutyric acid (GABA), a key neurotransmitter that inhibits activity in the CNS; or, the blocking of the activity of the excitatory neurotransmitter, glutamate. As epilepsies involve so many different underlying mechanisms, a single therapy will not be beneficial for all; tailored approaches are needed for the management of specific syndromes. Gupta et al., studied the effect of the selective cyclooxygenase-2 (COX-2) inhibitor etoricoxib on seizures, oxidative stress, and learning and memory, and reported that the anticonvulsant activity of the COX-2 inhibitor etoricoxib in pentylenetetrazole-kindled rats is associated with memory impairment. To elucidate the anticonvulsant effect of piperine and its mechanisms of action using in-silico, in-vivo, and in-vitro techniques, Mishra et al., used the parameterizer and analysis software system [PASS] to determine its possible activity and mechanisms. The latency for development of convulsions and mortality rate was recorded in different experimental mouse models of epilepsy with various doses of piperine. They evaluated the effect of piperine on Na(+) and Ca(2+) channels using the whole cell patch clamp technique. This study revealed that piperine decreased mortality in the maximum electroshock seizure (MES) model, delayed the onset of tonic-clonic convulsions on administration of pentylenetetrazole (PTZ), reduced associated mortality, and delayed the onset of tonic-clonic seizures. Finally, they proposed the Na(+) channel antagonist activity as a contributor to the complex anticonvulsant mechanisms of piperine. Another group evaluated the effect of bezafibrate as an anti-kindling agent in preventing the development of PTZ-induced seizures and suggested its potential for therapeutic applications in TLE. Talampanel was shown to be protective in kainic acid-induced neonatal status epilepticus model. Recently, N-[4-(4-(alkyl/aryl/heteroaryl)-piperazin-1-yl)-phenyl]-carbamic acid ethyl ester derivatives were designed, synthesized, and pharmacologically evaluated as novel anticonvulsant agents. Studies based on in-silico analysis reported computer-aided identification of sodium channel blockers in the clinical treatment of epilepsy and ligand-based drug design of new heterocyclic imines of GABA analogues in the discovery of new GABA-AT inhibitors.

Ayurvedic and botanical drugs

Almost 60 different herbs mentioned in Ayurveda literature have been studied for their antiepileptic activity. Asparagus racemosus root extract were shown to have ameliorating effect against pentylenetetrazol-induced kindling and associated depression and memory deficit. Aloe vera leaf extract were anticonvulsive in acute and chronic models of epilepsy in mice. Pahuja et al., reported effects of Anacyclus pyrethrum on pentylenetetrazole-induced kindling, spatial memory, oxidative stress, and rhokinase II expression in mice. Aqueous extract of Anethum graveolens leaves was shown to be effective in reducing the seizures induced by pentylenetetrazole in mice. Ethnomedicinal plants have been used for treating epilepsy by indigenous communities of the sub-Himalayan region of Uttarakhed. Anticonvulsant activity was found in the fraction isolated from the ethanolic extract of heartwood of Cedrus deodara. Ficus religiosa L. figs are shown to be potential herbal adjuvants to phenytoin for improved management of epilepsy and associated behavioral comorbidities. Glycyrrhiza glabra root extract showed anticonvulsant action and amelioration of oxidative stress in pentylenetetrazole-induced seizure in albino rats. Marsileaquadrifolia Linn showed antiepileptic properties in maximal electroshock and pentylenetetrazole-induced rat models of epilepsy. Black seed oil showed promising clinical outcome as adjuvant therapy in intractable epilepsies. Trichosanthes hispanica modulated oxidative toxicity in brain hippocampus against pilocarpine-induced status epilepticus in mice. Anticonvulsant activity of ethanol extracts of Vetiveriazzanioides roots and Zingiber officinale rhizomes extracts were reported in experimental mice. Curcumin was shown to be effective against pentylenetetrazol-induced seizure threshold in mice with the possible involvement of adenosine A1 receptors, and is antiepileptogenic in kainate-induced model of TLE; protective against lithium-pilocarpine induced status epilepticus, cognitive dysfunction, and oxidative stress in young rats; ameliorative against seizure severity, depression – like behavior, learning, and memory deficit in post-pentylenetetrazol-kindled mice. Curcumin supplementation improves mitochondrial and behavioral deficits in experimental model of chronic epilepsy. Withania somnifera and withanolide A. were shown to have ameliorating effects on impaired motor learning attributed to altered AMPA receptor function in the cerebellum of rats with TLE. Naveen et al., performed psychiatric analysis to show the positive effects of Yoga on epilepsy.

Optimising already existing treatments

With the aim of evaluating the effects of reducing the number of AEDs administered to patients with drug-refractory epilepsy (PRE) during their admission and documenting any change in seizure frequency in the subsequent follow-up, our group conducted a study on a total of 962 patients with PRE. Our study proved that optimization or reduction of the number of AEDs in patients with PRE leads to a reduction or to no change in seizure frequency with a significant decrease in adverse effects. The study of Suresh et al., compared the efficacy and...
Researchers continue to refine the efficacy of surgical outcomes in epilepsy. We have shown that intraoperative MRI (iMRI) improves the localization of the epileptogenic focus, and its impact on the patient and caregivers. Knowing when not to operate, because of the need for further investigations, is as important as selecting which patient may benefit from surgery in a resource-limited setting.[24] Recently, we have shown that administering a structured questionnaire in the preoperative evaluation may improve the localization of the epileptogenic focus.[24] Previously we have also shown that concordance between intraoperative SPECT and PET may be improved by the use of anesthetic techniques that suppress electrocorticography recordings.[23] We have also described our experience with the use of multimodal neuronavigation (fMRI and tractography) to facilitate surgical resection in TLE as well as in predicting the postoperative visual performance and disability.[64] We have also demonstrated that intraoperative MRI (iMRI) is as important as selecting which patient may benefit from surgery in selected cases of drug-resistant epilepsy (DRE). We have also described our experience with the use of multimodal neuronavigation (fMRI and tractography) to facilitate surgical resection in TLE as well as in predicting the postoperative visual performance and disability.[64] We have also demonstrated that intraoperative MRI (iMRI) is as important as selecting which patient may benefit from surgery in selected cases of drug-resistant epilepsy (DRE). Surgical management of epilepsy

Nearly one-third patients with newly diagnosed epilepsy on long-term follow-up will have their seizures unsatisfactorily controlled by treatment with available AEDs. Surgery remains an effective option for PRE. The types of surgery could be curative (resective surgeries: amygdalohippocampectomy, lesionectomy, and multilobar resections; functional surgeries: hemispherotomy) and palliative (multiple subpial transaction, corpus callosotomy, and vagal nerve stimulation). Epilepsy surgery in indicated cases has a success range of 50–86% in achieving seizure freedom compared with <5% success rate with AEDs in PRE.[65] Researchers continue to refine the surgical techniques to make them less invasive and to prevent cognitive and other neurological deficits that can result from surgery. In India, the three major comprehensive epilepsy surgery centers with advanced imaging tools such as magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), positron emission tomography (PET), and magnetoencephalography (MEG), as well as a multidisciplinary team of neurologists, neurosurgeons, neuroradiologists, electrophysiologists, psychologists, and psychiatrists operate at the All India Institute of Medical Sciences (AIIMS), New Delhi, NIMHANS, Bangalore, Christian Medical College (CMC) in Vellore, and Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTMIST), Thiruvananthapuram. Almost in the last two decades, these four centers have undertaken over 4000 epilepsy surgeries, out of which more than 2000 epilepsy surgeries were performed in AIIMS, New Delhi. The success of any epilepsy surgery program depends on the early identification of potential surgical candidates. Our group is extensively involved in research to refine surgery protocols. We have reported that the decision making for epilepsy surgery needs a multidisciplinary approach in which different investigators involved with the program work in conjunction to create an integrated picture of epileptogenesis and its impact on the patient and caregivers. Knowing when not to operate, because of the need for further investigations, is as important as selecting which patient may benefit from surgery in a resource-limited setting.[24] Recently, we have shown that administering a structured questionnaire in the preoperative evaluation may improve the localization of the epileptogenic focus.[24] Previously we have also shown that concordance between the non-invasive investigations, ictal SPECT (iSPECT) and fluorodeoxy glucose PET (FDG-PET) is an important predictive factor for surgical outcome in extra-temporal epilepsy.[77] We have also reported that delineation of ictal-onset zone (IOZ) by ictal-magnetoencephalography (ictal-MEG) helped to convert drug resistant epilepsy (DRE) patients unsuitable for surgery or planned for phase II monitoring into candidates suitable for surgery, even ECoG-guided resections, and resulted in favourable outcomes in those who were operated.[59] We have also described our experience with the use of anesthetic techniques that utilize an endoscope for performing a hemispherotomy and corpus callosotomy.[79,80] We have also described our experience with the use of anesthetic techniques that utilize an endoscope for performing a hemispherotomy and corpus callosotomy.[79,80] We have also described our experience with the use of anesthetic techniques that utilize an endoscope for performing a hemispherotomy and corpus callosotomy.[79,80]
Research progress in assessing the role of education in the treatment of epilepsy

Our recent study is one of the very few studies which have proven the efficacy of educational programs responsible for drug adherence in a population cohort with minimal educational background. This study paves the way to conduct a larger community-based study with a longer follow-up and more rigorous protocols for self-care management to assess the efficacy of health education in outcomes of drug adherence and self-care in PWE. Including these strategies will result in a holistic management of PWE, irrespective of their educational status. A recent study by Kolar et al. reports that the school-based health education programs for epilepsy awareness among school children are very important to bring changes in their attitude, behaviour, and practices. Even among the primary healthcare doctors, overutilization of EEG, improper prescription of AEDs, and inadequate skills in the management of AED-resistant epilepsies have been reported.

Research progress in understanding the process of epileptogenesis

Very few investigators in India are trying to understand the process of epileptogenesis to identify biomarkers to develop antiepileptogenic treatment. Previous studies in rats have shown that downregulation of 5HT2C receptors as well as NMDA RI expression in pilocarpine induced epilepsy in rats. The above mentioned studies were largely focused on the risk factors and genetic susceptibility to the disease. Kumar et al. looked at high levels of plasma apoE in TLE patients. The study was limited to a single protein, and further studies are required to identify novel biomarkers for TLE. Array-based profiling studies have shown implication of aberrant gene expression patterns in epileptogenesis. Venugopal et al. identified a set of genes that were differentially expressed in the surgically resected tissue from seizure zones when compared with the nonseizure zones in cases of intractable medial temporal lobe epilepsy (MTLE) due to medial temporal lobe sclerosis (MTS) using RNAseq approach.

Differential gene expression analysis of hippocampal tissues resected from patients with MTLE-hippocampal sclerosis (HS) using RNAseq approach. Venugopal et al. identified a set of genes that were differentially expressed in the surgically resected tissue from seizure zones when compared with the nonseizure zones in cases of intractable medial temporal lobe epilepsy (MTLE) due to medial temporal lobe sclerosis (MTS) using RNAseq approach. Differential gene expression analysis of hippocampal tissues resected from patients with MTLE-hippocampal sclerosis (HS) using RNAseq approach.

Research progress in reducing the comorbidities associated with epilepsy

Comorbidities or co-occurring psychiatric, neurodevelopmental, and sleep disorders are relatively common in individuals with epilepsy. In adults, depression and anxiety disorders are the two most frequent psychiatric diagnoses. Attention deficit hyperactivity disorder and anxiety frequently affect children with epilepsy. People with neurodevelopmental disabilities, such as autism spectrum disorder, attention deficit disorder, and learning disabilities, are known to be at higher risk for epilepsy. Seizures, despite being relatively brief in time, leave a dramatic impact not only on the quality of life of those who are living with them but also on those who witness them. Various functional magnetic resonance imaging (fMRI) language tasks (lexical reading, semantic decision, and semantic–syntactic processing) can cover important language components and guide surgeons for preservation of important functional brain areas during surgery. This will also reduce the development of comorbidities in these patients. Using fMRI as a tool, we have shown that impairment of memory, language, and executive function is common among patients with drug refractory epilepsy. The most prevalent impairment is in executive function. There is no significant difference in the degree, prevalence, or selectivity of impairment in either of the three domains, between the TLE versus ETLE groups. Srivastava et al., reported major depression and mixed anxiety depression as the most common neuropsychiatric manifestations in patients of NCC. In a population-based study, epilepsy was found in 23.7% of the children with intellectual disability, which was associated with a lower intelligent quotient score. Clinical studies revealed a higher frequency of psychiatric comorbidity in children with longer duration of seizures, increased frequency of seizures, poor compliance with medications, and especially, anticonvulsant polytherapy. Another study on women with epilepsy suggested that they are vulnerable to poor child rearing practices even after intervention. These comorbid conditions have the potential to alter the pharmacodynamics and pharmacokinetics of AEDs, or the AEDs and seizure itself can lead to the development of comorbidities. Hence, more basic research investigations are needed to explore these associations.
Future Research

As summarized in Table 1, studies carried out in India are mostly focused on the epidemiological aspects of epilepsy, genetic associations, or on identifying and validating new AEDs in animal models of epilepsy. Chronic epilepsies such as PRE lack effective therapies because of our lack of understanding of the cellular and molecular mechanisms that lead to aberrant neuronal network formations during the course of epileptogenesis. Many research groups across the world have examined the epileptogenic process to understand the different stages in this process. In animals, acquired epilepsy is studied most commonly with kindling models, status epilepticus models, and traumatic brain injury models. A recent study in animal model reported LAU-0901 as an AED, which limits kindling epileptogenesis and induces neuroprotection by antagonising PAF-r. This study suggested that PAF-r activation after brain injury is a key contributor to dysfunctional neuronal circuitry in epileptogenesis and may contribute to limbic seizures. In a recent paper, we reviewed various possible explored as well as unexplored epileptogenic markers that may also have the potential to serve as diagnostic/prognostic biomarkers of PRE. As none of the animal models for epilepsy could replicate the etiopathological conditions in humans, it is important to perform such studies in human brain tissues to conceptualize its role in epileptogenesis in humans. The well-defined resected brain tissue from focal epilepsy patients undergoing surgery are valuable and are ideal model systems for not only understanding the process of epileptogenesis but also for the development of novel biomarkers. Potential molecular biomarkers of epileptogenesis, including markers of inflammation, synaptic alterations, and neurodegeneration, may also have the potential for localizing the EZ. Identification of different steps in epileptogenesis will have benefits in clinical practice pertaining to either correct diagnosis or treatment. It may also help in the identification of patients who are at risk to develop chronic and sometimes refractory epilepsy. Early recognition and intervention could prevent chronic epilepsy in patients with epileptic seizures.

Conclusion

There is a need to increase the quality of epilepsy research in India to understand the underlying biology of epilepsy which will further aid in devising new treatments and cure for chronic epilepsies. National and international collaborations and support from funding agencies are needed to conduct quality research in India. Studies should focus on the use of underutilized resected brain tissues from focal epilepsy patients undergoing surgery to understand the process of epileptogenesis. Understanding the process of epileptogenesis may identify markers for early recognition and interventions for epilepsy.

Acknowledgement

This work mentioned in the article is supported by the grants Centre of Excellence for Epilepsy, a collaborative project between National Brain Research Centre, Manesar and All India Institute of Medical Sciences, New Delhi; Grant: BT/01/COE/09/08 and BT/Bio-CARE/07/9816/2013-2014 funded by Department of Biotechnology, Ministry of Science and technology, Govt. of India.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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