Recent Breakthroughs in Genetic Engineering and Environmental Medicine for Chronic Epilepsy

Article by Premkumar Krishnan
Clinical Research, Texila American University
E-mail: prem64@me.com

Introduction

Epilepsy has been with humankind from time immemorial. Yet with all the advancements made so far, a cure for Chronic Epilepsy has remained elusive. Even the symptoms cannot be controlled or managed in all cases. This has been the case not just for Chronic Epilepsy but all other chronic diseases.

In the fight against chronic diseases, Genetic Engineering is gaining a lot of emphases. And slowly the realization is dawning that probably Environmental Medicine may also be important. It is the replay of the old fight between Genes and Environment. What are the recent breakthroughs in the Aetiology, Diagnosis, Treatment and Prevention for Chronic Epilepsy? Is a cure in sight? And which is likely to triumph the Genes or the Environment?

Aetiology

Rapid progress has been made in trying to unravel the cause of chronic Epilepsy. However, at the present level of understanding, the knowledge is incomplete and not quite near to its root cause. It is incomplete because there is no solution to about one-third of persons suffering from this condition. And not quite near its root aetiology because the response to the remaining two-thirds is only reactionary and symptomatic (not predictive and preventive). There is no cure for Chronic Epilepsy as of date.

What is the aetiological journey so far and what to expect in the future? Is a cure for Chronic Epilepsy in sight?

The first aetiology

The word ‘Epilepsy’ is of its Greek origin means to ‘Seize’, to take hold of or to possess. Again, the word ‘Seizure’ is of Latin origin meaning the same as the word ‘Epilepsy’. These two words provides the first aetiology for this disorder - that a spirit possesses the sufferer. So deep is this causal belief even in present times (especially in developing countries) that in 1997, the World Health Organization (WHO), the International Bureau for Epilepsy (IBE) and the International League Against Epilepsy (ILAE) launched a global campaign to bring Epilepsy ‘Out of the Shadows’.

Subsequent aetiologies

The supernatural genesis of Epilepsy is prevalent to this day, but surprisingly the neurological underpinning of this disorder was known from the times of Hippocrates! Observing sacrificial sheep displaying terminal seizures, the cause of Epilepsy was maintained as the loss of blood to the brain. Today it is known that besides this vascular dimension of stroke, there are others - like brain injury, tumours, autoimmune, infection etc. which causes Epilepsy. These are classified as symptomatic, acquired or acute Epilepsy, and it is cured if the underlying cause is correctable.

However, most cases of Epilepsy are chronic, and in the beginning, it was thought to have a psychological origin. The similarities of some of the symptoms of Schizophrenia, many psychological comorbidities and certain epilepsies (Reflex Epilepsy) triggered by stimulus probably led to this conclusion. Today it is hypothesised that only Psychogenic Non-Epileptic Seizures (PNES) has a psychological aetiology. So, what causes Chronic Epilepsy?

Modern aetiology

Epileptogenesis has come a long way. It is now known that Epilepsy is caused by a recurrent and abnormal synchronous discharge of electric currents in the brain due to the imbalances in the inhibitory and excitatory neurons. These neuronal imbalances are caused due to faulty ion, ligand channels and

DOI: 10.21522/TIJCR.2014.SE.19.02.Art002
ISSN: 2520-3096

certain neurotransmitters. Today symptoms of almost 70% of Epilepsy patients is controlled through Anti-Epileptic Drugs (AEDs) only because of this aetiological understanding.

Promising future aetiologies

Two-thirds of Chronic Epilepsy is today treatable. Even in these cases, only symptomatic relief is possible with the cure being still elusive. This implies a long journey ahead in the search for the origin of this disorder. Recent developments in certain areas of science are holding a lot of promise both in the area of control and cure of Epilepsy.

Neuroscience - the neron-glia interactions

The human brain consists of two types of cells the neurons (nerve cell) and its surrounding glial cells. So far, the focus of the research was only on the neurons, and its mechanism with the role of glia assumed to be limited to repair, the supply of nutrients and as a packing material between neurons. But now the role of glial cells, especially astrocytes and microglia in the pathophysiology of Epilepsy is coming to light (Patel, Tewari, Chaunsali & Sontheimer, 2019). There has been an explosion of research in neuron-glia interactions and most of them are promising. Therefore soon, drugs targeting these new mechanisms can be expected.

It is hoped that these discoveries will at least provide symptomatic relief to the remaining one-third of the present refractory cases of chronic Epilepsy.

Genetics

The ‘Golden Standard’ for genetic epileptogenesis is the study of monozygotic twins (ideally raised in a different environment). Such studies strongly suggest syndrome specific genetic determinants for Epilepsy. Recent advances in technology facilitating massive parallel sequencing with international collaboration, have yielded a bounty of discoveries in the genetic architecture of Epilepsy. Some of the genetic surprise’s worth noting are de novo mutagenesis especially in epileptic encephalopathies, emerging evidence that Focal Epilepsy (long considered as an acquired condition) is genetic and the complex role of copy number variants especially in comorbid neurodevelopmental epileptic disorders (Meyers, Johnstone & Dyment, 2018).

These advances suggest that genetic testing is likely to become a standard in clinical settings very soon. This is already happening in some of the leading hospitals in epileptic care across the globe.

Epigenetics

The Genes are the root cause for the dysfunction in the neuronal and glial cell mechanisms. Understanding them would, therefore, take one closer to the goal of finding a cure (beyond symptomatic relief) of this malice. Today it is known that about 500 Genes are responsible for Epilepsy and metabolic dysfunctions. Yet that explains only about 8% of Epilepsy. What is the epileptogenesis for the bulk of the remaining cases?

There was a challenge at the beginning of this Century. The human cells make approximately about a lakh of different types of proteins. So, when the sequencing of the human genome began in 1990, it was expected that humans would have at least a lakh of genes, each coding for a particular protein. By 2003 when the project was complete and thorough subsequent revisions, it is now estimated that we had around 20,000 Genes only! A less biological complex C. Worm has about 24,000 genes, 4000 more than humans! How can the genetic code of the most evolved and complex human be smaller than the code of a less evolved worm?

That question in less than two decades has led to the presently burgeoning field known as epigenetics. It is a mechanism which sits over the genome and controls gene expression using DNA methylation, histone modifications and regulatory RNA. This permutations and combinations between the Genes and Epigenetics make the cell possible for the synthesis of a large number of proteins in the human body! The mechanism also provides for more significant interaction and adaptability with the environment (Non & Thayer, 2019). More importantly, Epigenetics proves that Genes are not destiny. Acquired traits can be inherited, and that environment and behaviour can change genes!

So, Epilepsy could have three possibilities based on the Gene-Environment interactions. A genetic determinist possibility - a faulty gene is expressing itself independent of the environment. Second environmental determinism - behaviours that could induce seizures in both humans and animal models with certainty (even 'chronic Epilepsy' can be induced in animal models!). And the third exciting possibility of the genetics and the environment interacting together, creating a predisposition to Epilepsy. The right environment and behaviours could prevent gene expressions, and disease manifestations and this trait can then be passed on to the next generation! The vast bulk of idiopathic Epilepsy seems to belong to this category. This is the area cut out for a new field of study called Behavioural Epigenetics.

The 'omics' revolution, bioinformatics and systems biology

Technologies like Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) and 'prime editing' both gene-editing tool, could rectify the faulty genome (acquired and de novo) and cure diseases. Coupled with Gene Drive, this could ensure that these corrections are inherited without errors to the whole of the population within a very short number of generations. This not only curing the individual but wiping out the disease in all future population!

However, as already mentioned diseases arising out of the changes in the genome form a small subset of our disease burden. The bulk of incurable diseases are chronic arising out of the environment and faulty behaviours. They appear out of changes made in the epigenetics mechanism in response to environmental changes and not in the genome sequence, which mostly remains unchanged during the life of a person. Can the epigenetic changes be described, understood, predicted and fixed?

Epigenetics has created an 'omics' revolution in molecular biology- Genomics (DNA), Transcriptomics (RNA), Proteomics (Proteins) and Metabolomics (Metabolites). These four 'omics completely describe a cell, and it's functioning. Also, two new specialities are emerging called Bioinformatics and Systems Biology. The Bioinformatics provides the snapshot knowledge of all the 'omics' while Systems Biology attempts to create models on how they all work together as a whole. Taken together, they offer the possibility of cracking the epigenetic code and find a cure for all diseases, including possibly Chronic Epilepsy (Mahoney et.al. 2019).

If in case this fails, an alternate direction for the solution is also known. So far, the focus is only on the protein-coding part of the DNA called exon. All the exons together constitute the exome. The hypothesis is that the exome holds the answer to all ailments. The exome is just 2% of the genome! The rest of it is presently called 'junk DNA' or 'dark matter'. May be researching the dark matter would provide us with the answers, if the current hypothesis fails.

In the end, a future where humans are capable of fixing both the genome and the epigenome is becoming a distinct possibility. The genomes determine Darwinian long term 'hard inheritance' while the epigenome controls Lamarckian 'soft inheritance'. The soft inheritance lasts for only a few generations as a temporary adjustment to the environment.

What would be crucial will be the ability and discipline to initiate and maintain healthy behaviours and habits and thereby control our epigenome. Correcting the epigenome but continuing unhealthy behaviours will only undo the correction and not have the desired outcome. Mastery over behaviours and not just genome and epigenome will provide victory in the fight against chronic diseases like Epilepsy.

In any case, exciting and hopeful times are ahead to play God and become masters of Destiny and not victims to Genes, Epigenetics or the Environment.

Diagnosis

Transient Loss of Consciousness (TLoC) with or without convulsions is the most common presenting symptom in the diagnosis of Epilepsy. However, TLoC is common to many other conditions. Broadly, the first step in the differential diagnosis is to rule out PNES. The next step is to ascertain whether the seizures are provoked or unprovoked. Finally, the diagnosis must zoom in on the epileptic nosology and then check if it fits into the fifty known and growing number of epileptic syndromes. Aiding the clinician in this diagnostic process are several recent developments.

DOI: 10.21522/TIJCR.2014.SE.19.02.Art002
ISSN: 2520-3096

Federated learning, automated history taking and a tRNA blood test

The technologies behind personal assistants, chatbots and artificial intelligence (AI) is exponential growing and is being increasingly used in basic scientific research and engineering. This is slowly finding its way into medicine, especially in the area of collecting and interpreting clinical data of a patient.

Real disruption is taking place in data collection, and it is beginning with Epilepsy research. Recently, doc.ai partnered with Stanford University for clinical research in Epilepsy (Thomas, 2019). This project is a 'proof of concept' for a radically new technology called 'Federated Learning' in AI. The processing power of its new AI platform with the convenience of using mobiles for data collection has the potential to change clinical research forever. So far data collection for research purposes did not get traction due to privacy and ownership issues of data. The new technology maintains privacy and also allows for patients to own their data which incentivizes them to share theirs with the researchers willingly. A real win-win for both. This technology is expected to disrupt the whole of 3.5 trillion-dollar health care industry! More importantly, fixing the privacy issue would make more of such data turn digital and readily available for software like automated history taking, for effective diagnosis.

Automated History Taking is now considered to be the second generation of Electronic Health Record (EHR) technology. This has now become possible because of its ability to harness AI for speech recognition through personal assistants and chatbots. Besides this AI is now used for interpreting medical data and arriving at a probable diagnosis. It is done using diverse data from history taking, blood and imaging reports. In some of the cases, the programs are found to be more accurate than humans. In other cases, they can discover even new patterns expanding the present knowledge on the diagnosis. A surprising advantage of using these AI machines is that they keep becoming better with time. Because their learning improves as they are fed more and more data (Stuttgart, 2019).

One such program which is currently gaining traction is the Clinical Expert Operating System (CLEOS). CLEOS is an automated history taking the program. It is gaining more popularity relative to its competition because of its decision-making feature. CLEOS emulate clinical thinking and differential diagnosis continuously as it is collecting and validating data! Even though such a program is not yet available for Epilepsy, there are several in the pipeline with some of them attracting generous project grants.

Another stunning development in Epilepsy diagnosis is a distinct possibility of seizure detection with just a blood test. Researchers have found a spike in a molecule called transfer RNA (tRNA) hours before the onset of a seizure. tRNA is involved in coding of protein, and it has been found that their activity increases as the brain gets ready for a seizure. Today their measurement in blood requires a large sample of plasma blood (Hogg et.al, 2019). Further development in this area could result in the test being done with just a small drop of whole blood. Research in this area could also offer clues on the aetiology.

Federated learning, automated history taking, a simple blood test and telemedicine would catapult clinical examination and diagnosis to a new height. In most parts of the underdeveloped or developing countries, which do not have access to advanced diagnostic testing, a proper clinical examination is their only hope for a minimal and humanized Medicare. Because of this reason, one can expect more flow of resources in the development of these technologies in the coming future.

Advances in genetic screening

The human genome project was an international research project to map the entire human genome. It took about 13 years to complete and cost 2.7 billion US Dollars (USD). By 2014-15 due to technological advancements, the same could be done within a day for just 1000 USD. We are rapidly approaching the next milestone to be able to do the sequence of the whole human genome within an hour for only around 100 USD!

Even at the 600 USD current price point, it is almost one fourth the cost of an MRI. This next-generation sequencing replaces the earlier Sanger sequencing. Three types of tests are ordered, namely Whole Genome sequencing, Exome sequencing and Targeted gene panel sequencing. Since exome sequencing is just 1% of the genome, the cost is significantly lower. It is even lower for targeted gene panel sequencing.

Advances also have taken place in spotting chromosomal defects. The earlier Karyotyping is replaced by Comparative Genome Hybridization (CGH). This test has a much higher resolution for detecting duplication and deletions indicated by the copy number variants.

Continuing technological advances are making these tests faster and cheaper. Genetics testing for Epilepsy is becoming more accessible and is already the first-line diagnostic tool in clinical settings of many leading hospitals in the world.

Advances in neuroimaging

The current Gold Standard in the diagnosis of Epilepsy is Electroencephalogram (EEG). Recent advances in this area have been a game-changer. Take, for instance, the FDA approved Ceribell^{TM}- Rapid Response EEG. It is effortless and fast to set up and takes an EEG of a patient within 6 minutes with instant auditory diagnostics. This is a portable device, and any nurse could be trained to operate it. Conventional equipment is expensive, time-consuming and requires a qualified radiologist. This machine is 97% accurate compared to the conventional ones!

Ceribell has the potential of becoming the stethoscope of every epileptologist in the coming future (Gururangan & Parvizi, 2019). Another primary application is in its role that it can play in the Emergency Room (ER). Status Epilepticus (SE) is a dangerous condition requiring timely and strict protocol in the ER room, else severe brain damage or even death could arise. As a part of the protocol, an EEG of the patient may be required. One could already see the limitation of the conventional EEG machines to carry out this, especially wherein the time is of crucial importance. Therefore, it is easy to see how devices like Ceribell could become a part of any ER.

However, there is a problem with the EEG taken with the electrodes placed on the scalp. These cannot pick up signals emanating from the deep subcortical structures of the brain. This necessitates invasive intracranial EEG (iEEG) or at least the minimally invasive stereo EEG (sEEG). Is it possible to listen to the electrical signals emanating from any parts of the brain non-invasively? Yes, Magnetoencephalography (MEG) solves this problem. However, these machines are more expensive and bulkier, like Magnetic Resonance Imaging (MRI). Not many hospitals nor most patients can access this. Are there any solutions in sight for solving this problem?

The cost and bulk of these MRI and MEG machines are mainly because their Super Cooled Liquid Helium sensors called SQUIDs. These are required to create a strong magnetic field which makes them do their job. New types of sensor called the Optically Pumped Magnetometers (OPMs) are showing promise to replace the SQUIDs. These are cheap and small enough to make future MRI and MEG machines portable! These are not something to happen in a distant future, prototypes of mobile MEG devices are already available (Boto et.al, 2018)!

Nanotechnology is another exciting field which could replace neuroimaging or MRI imaging. Radioactive materials are used currently as contrast, to enhance MRI imaging in some cases, notwithstanding its harmful radiation effects. Plasmonics is light-activated semiconductors and graphene nano-sensors which could replace these harmful contrasts. These sensors are expected to be widely used to study both the anatomical and physiological functions of biological entities down to the neuronal or the cellular level in the future.

An innovative diagnostic underdog

The increasing awareness of Sudden Unexpected Death in Epilepsy (SUDEP) is making many go for a Service Dog, especially for those living alone. Service dogs have been used by epileptic patients to detect and warn them about their seizures for a long time. However, only at the beginning of this year 2019, their effectiveness in detecting seizures was scientifically validated (Catala, Grandgeorge, Schaff, Cousillas, Hausberger & Cattet, 2019). The sensitivity and specificity obtained were among the highest as shown by any other such studies. This indicates that despite different types of epilepsies and individual body odours, Epilepsy is associated with a very definite Olfactory Profile!

It is also known that the trained dogs can predict the onset of the seizures even 45 to 60 minutes in advance. Research is now on to prove if this is indeed scientifically valid. If found true, pair it with the current advancements in the electronic nose (e-nose) and AI, the potential birth of a revolutionary diagnostic tool for seizure prediction and detection becomes apparent.

DOI: 10.21522/TIJCR.2014.SE.19.02.Art002
ISSN: 2520-3096

Automated history taking and next-generation genetic screening are excellent diagnostic tools. Portable neuroimaging with a high spacial and temporal resolution for assessing the structural and functional integrity of the human body would take bedside clinical diagnosis to a level not just for Epilepsy diagnosis but for any disease requiring imaging.

But the most exciting among these diagnostic tools are the Epilepsy service dog and the tRNA blood test. Besides their unique predictive diagnostic prowess, they could offer a paradigm-shifting perspective on the underlying aetiology of Epilepsy. The tRNA blood test is likely in about five years. Until such time, there is no denying the role of a Service Dog. The dog is not merely the friend of humans but the best friend for a Refractory Epilepsy (RE) patient offering them unmatched seizure detection, prediction and peace of mind. Genuine innovations need not be something technologically advanced and sophisticated. It can be as simple as a Service Dog!

Treatment

Epilepsy is currently treated using Anti-Epileptic Drugs (AEDs), surgery and neural electrical stimulation devices. So far, it is possible to only control/manage the symptoms. Barring a very few surgical cases, a cure for the rest is still elusive. Even while managing the symptoms, we are failing in nearly one-third of the cases. Will the recent breakthroughs potentially change this scenario? And, which treatment modality is likely to emerge as the most promising?

Neural electroceuticals

Electroceuticals are emerging as the Third Force (besides drugs and surgery) as a treatment of choice. Many crucial body organs like muscle, heart and brain etc. work with electricity. Human bodies naturally generate electrical fields during the healing process. Electrical bandages are already proving to be more effective than conventional ones. Electroceuticals are now routinely used to treat migraines, chronic back pain, urinary/faecal dysfunctions and Epilepsy.

Using electricity for the treatment of the medical condition has had a long history. Along the way, it fell out of favour and is now re-emerging as a new treatment option. Electrostatic Convulsion Therapy (ECT) is used to induce seizures and is continuing to be used as the treatment of last resort for depression and schizophrenia. Electric shock therapy is employed to revive the heart and brain. If all protocol in the management of Status Epilepticus (SE) fails, then an electric shock is used to revive the brain and save the patient.

Neural electroceuticals are used only in the treatment of RE cases. Popular devices are Liva Nova™ for Vagus Nerve Stimulation (VNS) and Deep Brain Stimulations (DBS) from Medtronics™. The new kid on the block is Neuropace™. Neuropace is the pacemaker for the brain and uses Responsive Nerve Stimulation (RNS). These detect the exact region of seizure zones in the brain and respond to them to silence it (Markert & Fisher, 2018).

Despite these advances, they seem to work only in one-third of the patients as of now. And is considered only in patients for whom both drugs and surgery has not worked or workable. But there are other projects in pipeline promising better outcomes. In October 2019, Cadence Neuroscience™ raised 15 million USD for an electroceutical treatment of Epilepsy created at the Mayo Clinic. The new technology is expected to have a much better outcome.

Research is on, and with their ability to target specific parts of the body, growing miniaturisation of devices, biodegradable designs and fewer side effects, electroceuticals could find itself as the first-line treatment choice in the coming future.

Surgicals

About 10% of people with RE become suitable for surgery. Eligible candidates are those who have a localised focal onset on one side of the brain and whose removal does not compromise regular functioning. Surgeries have become safe, and for the qualifying patients, this is the only treatment which offers hopes of a complete cure - complete freedom from seizures in most cases!

The first step is in locating the exact focal zone of the seizure. This is now done using minimally invasive robot enhanced Steroelectroenphalography (sEEG) neurosurgery.

Once the part to be resected is identified, a choice is to be made between invasive and non-invasive surgical procedures. Under invasive methods, remote-controlled soft, flexible robotics is gaining popularity. In contrast to robots built with rigid materials, soft robots allow for increased flexibility, manoeuvrability, accessibility and safety in working with living systems. These machines are not yet sophisticated enough to operate on the brain but are now used in operating the lungs.

Laser and Ultrasound Ablations were the mainstays in the non-invasive epileptic surgery; however, Gamma Knife radiosurgery is gaining popularity. This type of radioactive incision is very sharp, and there is a clear delineation between the dead neurons and the healthy neurons with very few damaged neurons. Since damaged neurons cause surgery-induced problems, this type of surgery offers better outcomes (Romanelli & Conti, 2019).

Stretching the non-invasive surgery into the future is Nanosurgery and Nanobots. Nanosurgery uses fast laser beams to exert a controlled force in manipulating subcellular structures. Nanobots are robots made up of nanomaterials that can carry out tasks. They are presently used in research as DNA probes, cell imaging materials and cell-specific delivery vehicles. These technologies in the future would enable us to remove, build or repair a particular neuron, glial cell or any cell!

Surgery could also benefit in a new direction with the advancements in virtual reality, augmented reality, mixed reality and 3D printing (Ye, 2019). These technologies can help surgeons in learning and in performing surgery in a simulated environment and then operating the exact 3D printed replica of the patient's brain before the actual operation (Camaraderie, Panov, Oemke, Ghatan & Costa, 2019)! Other industries like aviation are already using it. It is time for the medicine to exploit these advancements. All these technologies can also make telesurgery a reality!

Pharmaceuticals

Pharmaceuticals currently are the first line of treatment modality for Epilepsy. In about 70% of the patients, their symptoms can be controlled. There is hope that with the current research implicating the role of glial cells with the neurons, one could soon expect drugs exploiting these mechanisms and hopefully control symptoms in all Epilepsy patients.

In March 2016, Spritam™ (levetiracetam) became the first FDA approved 3D printed drug. The tablet is used to treat Epilepsy. The trend is likely to continue with customized dosages (no few sizes to fit all) and 3D printing of multiple drugs in one pill for better drug compliance. When equipped with ingestible Radio Frequency Identity (RFID) tags, this could provide timely third-party warnings of non, under, overdosing of drugs.

Recently FDA approved a new drug with Cannabidiol (CBD) - a non-psychoactive drug derived from the cannabis plant. Clinical trials found it to be useful for treating two rare forms of Epilepsy, namely the Lennox-Gastaut syndrome and Dravet syndrome (Laut et.al, 2019). If the drug turns out to be effective, then there is a problem in producing large amount of this compound through conventional farming due to its low yield. A similar issue was faced when the hormone insulin was discovered. This was the first golden molecule of the biotech industry. Using recombinant DNA technology on bacteria or yeast, insulin was produced in large quantities. Many companies are trying to do the same to mass produce the CBD compound. These technologies have been God-sent for the pharmaceuticals industries and make these low yield compounds a non-issue in creating these new Anti-Epileptic Drugs (AEDs).

The real excitement, however, is in an emerging field called Pharmacogenetics (Bozina, Klarica-Domjanovic, Tvrdeic & Sporis, 2019). Today there are about 70 odd AEDs for the treatment of Epilepsy. These drugs have to be tried on a trial and error basis on the patient to zero in on the right medication and dosage with minimal toxicity. Most of these drugs have withdrawal effects; hence, this whole process is painful and time-consuming. Advancements in stem cells and cloning is now made it possible to carry out this trial and errors process in petri dishes using the patient's neuronal cells to zero in on the right AED (monotherapy) or AEDs (if polytherapy drug therapy is warranted) with minimal side effects in a short period! This will usher in an era of truly personalized and precision medicine. The method allows for the testing of multiple drug interactions specific to the patient. This was not possible to do until now.

DOI: 10.21522/TIJCR.2014.SE.19.02.Art002
ISSN: 2520-3096

Gene therapy and regenerative medicine

Fixing the mutated disease-causing gene, of the human genome using CRISPR ("prime editing" is a recent breakthrough innovation in gene editing) and Gene Drive is no longer science fiction (Ledford, 2019). This is now an FDA approved treatment modality for certain type blood cancers. Its use in other diseases and Epilepsy is a distinct possibility in the coming future.

In March 2019, Italian surgeon Sergio Canavero announced the world's first human head transplant on a corpse after successfully experimenting this procedure on mice, dogs and primates (Ren, Kim & Canavero, 2019). At the press conference, he said that an operation on a live human being would be imminent! It is now possible to transplant most parts of the human body except for the brain. It will be a monumental achievement in medicine and for humanity to clone and transplant a 'seizure-free brain'!

While organ cloning and transplant, especially of the brain might be a distant dream, phenomenal advancements have been made in cloning and transplanting tissues in regenerative medicine. It has found its way from research labs to clinics to treat some conditions like blindness and knee cartilages. One could look forward to the replacement of damaged seizure causing neural tissues of the brain as a treatment for Epilepsy in the future.

Digital therapeutics

Digital Therapeutics (DT) uses the software as medicine. It is the new kid in the block. Such products must undergo the same level of clinical rigour to prove its efficacy and safety as any pharmaceutical drug. In August 2018 FDA created a separate regulatory pathway called Software as Medical Devise (SaMD) for any DT product seeking its approval. DT can be used to complement and enhance conventional therapies mentioned above. Epicadence^{TM} is one such DT product used for treating Epilepsy (Metcalf et.al, 2019).

DT products are useful as a high touch tools for connection with the health care professionals, care givers and the community. They ensure proper understanding, adherence and accountability to the treatment protocol resulting in better treatment outcomes. More of such products could be expected in the future. This is just the beginning.

Management of treatment-resistant epilepsy

The year 2019 saw two noteworthy awards given away both for the management of RE. The TLoC with or without convulsion makes a patient avoid public places and not carry out certain activities like swimming, driving etc. severely compromising the quality of life. The Microsoft Global Hackathon awarded the grand prize winner to project Mirror-HR (an Epilepsy Research Kit for Kids). This consists of a wearable device paired with a mobile app and alerts parents or caretakers as and when a seizure takes place. Later in the year, James Dyson design award was given for the invention of a unique portable epileptic seizure protection and an alert device called Cocoon^{TM}. The future version of this device is expected to be fitted with sensors to track seizure duration, intensity and frequency.

A Cocoon, a paired wearable watch and a service dog, are the best measures at the moment for managing Treatment-Resistant Epilepsy.

Among all the treatment modalities in development for Epilepsy, a realistic expectation timeline would be the possibility of controlling the symptoms in all refractory cases with new AEDs targeting the glial cells. We have almost accumulated two decades of promising research in this area, and new drugs in direction appear to be a distinct possibility. Next is the possibility of electroceuticals becoming a first-line option replacing the drugs and surgery with minimal side effects. Both this development could, at best control Epilepsy fully. However, the hope for curing Epilepsy is likely only with the advancements to be made in Gene Therapy and Regenerative Medicine.

Prevention

Medicine is slowly moving away from its reactionary mode of waiting for a disease to happen and then treating its symptoms, to what is now being called the P4Medicine. This is a new paradigm. The 4 Ps of this paradigm represents Prediction, Prevention, Personalization and Participation.

Epilepsy is a chronic disease. It unlike other chronic diseases like cancer, diabetes, obesity etc. is not a growing epidemic. It is estimated that about 50 million suffer from this condition globally. Its prevalence is about 1%. The percentage is small and stable. Is Epilepsy a very different type of chronic disease? Is Epilepsy all about genetics and genetic determinism with the possibility of only control or cure at best and with no hope for prevention?

Genetic/epigenetic screening and therapy

The genetic causes for both provoked and unprovoked epileptic seizures is a small percentage which is less than ten per cent. The best hope for such people is a cure with gene therapy. Prevention for them would be in the form of helping them stop future generational transference. This could be done by the genetic screening of the fertilized eggs and then selecting and nurturing only those that are defect-free. This method could prevent not only Epilepsy but all other inheritable diseases in the future population.

The bulk of others with Epilepsy have a potential epigenetic aetiology - a propensity or predisposition to the disease. In people predisposed to Epilepsy, certain behaviours or events like head injury, triggers seizures. These, however, do not trigger seizures in the rest of the population. What could be the prevention in such cases?

Prevention in these cases is by first successfully screening for people with predisposition using epigenetic markers and then possibly fixing them with epigenetic therapy so that they become hardy like rest of the normal population.

That is certainly a very hopeful and positive vision for the distant future.

But what are the preventive measures we could presently take now, with no way to epigenetically screen and fix predisposition? The trick is to assume that one may be predisposed and adopt a healthy diet and lifestyle behaviours. This will be the antidote against not just Epilepsy but all other chronic diseases.

Lifestyle interventions

What are some of the main environmental factors that trigger Epilepsy or for that matter, any chronic disorders? The answer to that is simple.

1. Avoiding head injuries by wearing helmets, seat belts during driving and avoiding high impact sports like rugby or boxing. Brain lesion results in seizures.
2. Avoiding chronic stress with adaptive coping mechanisms, meditation and adequate restful sleep. Stress and sleep deprivation easily trigger seizures.
3. Avoiding drugs and alcohol abuse. Binge drinking followed by withdrawal results in status epilepticus!
4. Avoiding junk food and eating a healthy balanced diet. Hypoglycaemia induces a seizure. A diet low in carbs like the paleo and keto is very friendly for brain rehabilitation.
5. Avoiding toxins from the air, water, food, cosmetics and other chemicals. Carcinogenic substances cause Cancer. Cancer, especially of the brain, can trigger seizures.
6. Avoiding sedentary lifestyle and engaging in cardiovascular, strength and flexibility exercises with adequate exposure to the sun. Cardiovascular diseases can result in strokes leading to seizures.

While the answer to ‘What is to be done to prevent epilepsy?’ is simple, its execution is not that simple. We have a growing epidemic of chronic conditions like cancer, heart disease, diabetes, obesity etc. It is often not the lack of knowledge which is the issue. Inability to do what is right, is the central issue. How to make this happen? The first step in the process is to get an advance warning when something wrong begins to happen in the physiology. What provides an advance feedback?

Round the clock monitoring using digiceuticals

In the future rapid advancements in the ‘omics’, bioinformatics, systems biology, Internet of Things (IoT), mobile technology, AI etc. would usher in an era wherein digiceuticals track real-time epigenetic changes and warn us of disease well before the symptoms develop! That would take preventive medicine to the next level.

DOI: 10.21522/TIJCR.2014.SE.19.02.Art002
ISSN: 2520-3096

Currently, portable 'devices' like mobiles, 'wearables' like smartwatches, 'embeddables' like pacemakers or neuropace, 'printables' like 3D printed pharmaceuticals, herbaceuticals or nutraceuticals and 'ingestibles' like RFID pills are emerging as the first point contact for preventive healthcare. They warn physiological changes in the body, motivating one to go in for more advanced diagnostic investigations.

Advanced functional diagnostics testing

Advanced functional diagnostics uses saliva, blood, urine and stool samples to identify the root causes in physiological functioning of the body system. These tests can locate functional issues in various biochemical pathways in our neuroendocrine, gastrointestinal and detox pathways etc. It can also identify dysfunctions in the exact metabolic intermediaries.

Such tests are not yet mainstream but is gaining popularity. Genova Diagnostics™ is one of the many such companies. If knowing something is wrong is the first step, then knowing what exactly is the problem using advanced functional diagnostics is the next step in the new paradigm of preventive medicine. What is next? How to fix the problem? Not the usual pharmaceuticals, surgicals or electroceuticals. There is a surprise here.

Herbaceuticals, nutraceuticals and lifestyle interventions as medicine

Advanced functional diagnostics is the part of something called Functional Medicine (FM). Unlike main stream medicine, it has a strong slant towards curing and prevention of chronic conditions. FM's effectiveness has made leading medical care center like Cleveland Clinic to start a separate wing for it. Also, FM is unique and different from the mainstream in the way it fixes problems. It resorts to using Herbaceuticals, Nutraceuticals and Lifestyle Interventions as medicine!

Chinese and Indian medicine traditionally had used herbs (besides diet and lifestyle) for thousands of years. They were the first line of defense with the onset of any prodromal symptoms or was taken regularly as a prophylactic, for vitality and well-being (e.g. curcumin with no culinary benefit is a part of many Indian cuisines). One such herb now gaining a lot of press relevant to Epilepsy is Cannabis.

Cannabis or Marijuana is a psychoactive but also a terrific medicinal plant. Dr Sanjay Gupta's 'Weed' series on CNN has made this herb a household name in the US and globally. Its consumption is becoming legal in many states in the US. It has compounds which are clinically proven to treat certain types of epilepsy. Now clinical trials are being carried out for its effectiveness in treating Autism. Traditionally and anecdotally, they are used in a wide range of medical conditions such as migraine, chronic pain, rehabilitation for cancer chemotherapy, opioid rehabilitation and many other neurological issues.

One way to research this herb is the reductionist approach of pharmaceuticals. Strip the herb of its compounds and test for its effectiveness. Is this the best approach? Israel is the Mecca of research on marijuana and pioneering it is Raphael Mechoulam. Raphael Mechoulam is known as the father of marijuana research. He says that a lifetime is inadequate to research the many compounds of this herb. More importantly, he says that the most under-researched but potentially promising area is how the many compounds of marijuana compounds work together to produce their known effects. That insight, to shift the perspective from the parts to the whole completes the circle of the old and the new and highlights the importance of herbaceuticals as propounded by the ancient medical traditions.

The effectiveness of the herbs is influenced by their type of breeds and their growing conditions. With the advancements in aeroponics, vertical farming, AI-controlled environment and genetic plant breeding, the future could see the modern FM strengthen the traditional and revive herbaceuticals for treatment and disease prevention.

Besides herbaceuticals, FM extensively uses nutraceuticals. FM uses nutraceuticals only as a short-term relief. It serves as a gentle nudge towards initiating diet and lifestyle changes which is the main arsenal of FM to treat and prevent chronic diseases on a long-term basis!

For example, an advanced functional biome test could show lack of specific commensal bacteria in the gut biome, causing low Short Chain Fatty Acids (SCFA). This can motivate one to take polyphenol and fibre supplements. The nutraceuticals provide short term relief, which convinces the patient to take diets rich in these compounds. This works much better than just advising the patient to eat healthy food with a lot of fruits and vegetables at the outset.

Is digiceuticals and FM adequate to know what is right for prevention and be motivated to adequately do actions and turn it into a healthy habit?

Preventive digital therapeutics

FM and digiceuticals are not adequate to motivate right action. Taking the right action is difficult and not doing the wrong actions is even more difficult. Overcoming unhealthy habits and adopting healthy ones, therefore, becomes the real core element of preventive medicine. Preventive DT offers potential help in this regard. Unlike the normal DTs, preventive DTs are standalone software products.

An ideal preventive DT product would recognize the importance of lifestyle interventions and the challenges of behaviour modification. Such a product would use state of the art third-wave behavioural therapies as its core preventive element while having multiple diagnostic features for various chronic diseases like Epilepsy. This is done to set the baseline, monitor progress and ultimately prove its efficacy. As more and more people start using it, these products using AI would only become better and better over time.

However, there is no product for Epilepsy prevention as of now. The closest preventive product is called Neurotrack™ for diagnosing memory and preventing Alzheimer. Even though the diagnostic component of the software is not tailored for epilepsy, the preventive part can be used by anyone for maintaining good brain health. The technology and the time are right for the imminent birthing of such a preventive DT product for epilepsy.

So, what would have played a crucial role in the prevention of Epilepsy or any chronic disease and ushered in a true era of P4Medicine? At the face of it, Epigenetics would appear to walk away with the honours. Yes, future advances in Epigenetics would make it possible for screening people predisposed to Epilepsy and fix them by making them as hardy as an average person. But Epigenetics is a two-way process. Wrong behaviours would undo the fixes, thus compromising prevention and making them vulnerable to chronic diseases once again. Therefore finally, the real crucial element for prevention would be the mastery over behaviours, not genes, Epigenetics or the environment. The others would, at best, play a supportive role only.

References

[1]. Boto, E., Holmes, N., Leggett, J., Roberts, G., Shah, V., Meyer, S. S., Munoz, L. D. & Brookes. M. J. (2018, March 29). Moving magnetoencephalography towards real-world applications with a wearable system. *Nature*. Retrieved from https://www.nature.com/articles/nature26147.

[2]. Bozina, T., Klarica-Domjanovic, K., Tvrdeic, A., & Sporis, D. (2019 October 7). Pharmacogenetics and the treatment of epilepsy: what do we know? *Future Medicine 20*(15). Retrieved from https://www.futuremedicine.com/doi/10.2217/pgs-2019-0085.

[3]. Camara, D., Panov, F., Oemke, H., Ghatan, S., & Costa, A. (2019 January). Robotic surgical rehearsal on patient-specific 3D-printed skull models for stereoelectroencephalography. (SEEG). *International Journal of Computer Assisted Radiology and Surgery 14*(1). Retrieved from https://link.springer.com/article/10.1007/s11548-018-1885-5.

[4]. Catala, A., Grandgeorge, M., Schaff, J., Cousillas, H., Hausberger, M., & Cattet, J. (2019 March 28). Dogs demonstrate the existence of an epileptic seizure odour in humans. *Nature*. Retrieved from https://www.nature.com/articles/s41598-019-40721-4.

[5]. Gururangan, K., & Parvizi, J., (2019 August 14). Midline and Parasagittal Seizires are Rare in Adult Patients. *Neurocritical Care*. Retrieved from https://link.springer.com/article/10.1007/s12028-019-00804-6.

[6]. Hogg, M. C., Raoof, R., Naggar, H. E., Monsefi, N., Delanty, D. F., O'Brien, D. F., Rosenow, F. & Prehn, J. H. M. (2019 April 30). Elevation of plasma tRNA fragments precedes seizures in human epilepsy. *Journal of Clinical Investigation. 129*(7). Retrieved from https://www.jci.org/articles/view/126346.

[7]. Laux, L. C., Bebin, E. M., Checketts, D., Chez, M., Flamini, R., Marsh, E. D., Miller, I., Nichol, K.& Weinstock, A. (2019 August). Long-term safety and efficacy of Cannabidiol in children and adults with treatment resistant Lennox-Gastait syndrome or Dravet syndrome: Expanded aces program results. *Epilepsy Research 154*. Retrieved from https:www.sciencedirect.com/science/article/pii/S0920121118305837.

[8]. Ledford, H. (2019 October 21). Super-precise new CRISPR tool could tackle a plethora of genetic diseases. Nature. Retrieved from https://www.nature.com/articles/d41586-019-03164-5.

DOI: 10.21522/TIJCR.2014.SE.19.02.Art002
ISSN: 2520-3096

[9]. Mahoney, J. M., Mills, J. D., Muhlebner, A., Noebels, J., Potschka, H., Simonato, M., & Kobow, K. (2019 May 14). 2017 WONOEP appraisal: Studying epilepsy as a network disease using systems biology approaches. *Epilepsia, 60*(6). Retrieved from https://onlinelibrary.wiley.com/doi/abs/10.1111/epi.15216.

[10]. Metcalf, C. S., Huntsman, M., Garcia, G., Kochanski, A. K., Chikinda, M., Watanabe, E., Underwood, T., & Bulaj, G. (2019 March 27). Music-Enhanced Analgesia and Antiseizure Activities in Animal Models of Pain and Epilepsy: Towards Preclinical Studies Supporting Development of Digital Therapeutics and Their Combinations with Pharmaceutical Drugs. *Frontiers in Neurology 10*. Retrieved from https://www.frontiersin.org/articles/10.3389/fneur.2019.00277/full?fbclid=IwAR0Fulsn
Teim_a9OGk8zM4JUlH27dnWvXR6Ov9Bf7tAOSU8y_a_QNz4d8.

[11]. Myers, K. A., Johnstone, D. L., & Dyment, D. A. (2018 July 10). Epilepsy genetics: current knowledge, applications, and future directions. *Clinical Genetics, 95*(1). Retrieved from https://onlinelibrary.wiley.com/doi/full/10.1111/cge.13414.

[12]. Non, A. L., & Thayer, Z. M. (2019 March 8). 'Epigenetics and Human Variation' in D. H. O'Rourke (Ed.), *A Companion to Anthropological Genetics*. Wiley-Blackwell. Retrieved from https://onlinelibrary.wiley.com/doi/abs/10.1002/9781118768853.ch19.

[13]. Patel, D. C., Tewari, B. P., Chaunsali, L., & Sontheimer, H. (2019 February 21). Neuron-glia interactions in the pathophysiology of epilepsy. *Nature Review Neuroscience, 20*. Retrieved from https://www.nature.com/articles/s41583-019-0126-4#auth-1.

[14]. Ren, X., Kim, C., & Canavero, S. (2019 March 26). Bridging the gap: Spinal chord fusion as a treatment of chronic spinal cord injury. *Surgical Neurology International.* Retrieved from https://drive.google.com/file/d/1C-ZyjnS0eL8tjdkSVsq5psqRf3aC4Vav/view.

[15]. Romanelli, R., & Conti, A. (2019). Image-Guided Robotic Radiosurgery for the Treatment of Drug Refractory Epilepsy. *Epilepsy Surgery and Intrinsic Brain Tumor Surgery*. Retrieved from https://link.springer.com/chapter/10.1007/978-3-319-95918-4_20.

[16]. Stuttgart, G. T. (2019). Role of Artificial Intelligence within the Telehealth Domain. in Craig, K. (Ed.) *Year Book of Medical Informatics*. Retrieved from https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0039-1677897?device=mobile&innerWidth=980&offsetWidth=980.

[17]. Thomas, A. (2019 October 16). Health Care Startup Doc.ai Announces New Digital Trial and Lays Blueprint for Changing the $3.5 Trillion Health Care Industry. *Inc*. Retrieved from https://www.inc.com/andrew-thomas/healthcare-startup-docai-announces-new-digital-trial-lays-blueprint-for-changing-35-trillion-healthcare-industry.html.

[18]. Ye, Z. (2019 October 9). Mixed Reality breaths fresh energy into the development of modern surgery. *Global Health Journal*. Retrieved from https://www.sciencedirect.com/science/article/pii/S2414644719300521.