Epilepsy: A Neurological Disorder

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ABSTRACT

Epilepsy, although one of the most common neurological disorders with relatively high associated economic costs, is one of the most overlooked and underfunded neurological conditions. As a result, Epilepsy is a widely misunderstood affliction and thousands of lives are affected as a result. Moreover, with no known cure, Epilepsy is a condition with an alarmingly high mortality rate whereby the brain produces sudden bursts of electrical energy that can interfere with a person's state of consciousness, movements and/or general sensations. This paper focuses on the different current treatments for Epilepsy, including both modern and alternative medical approaches. It also looks at the different types of seizures as a determinant and to classify the different kinds of epilepsy. This paper addresses the impacts this condition has on the lives of the afflicted and what current studies are being carried out to discover the underlying cause(s). It is on the basis of these findings that we will be able to conclude the ways in which we can work towards preventing them and eventually, a cure.

INTRODUCTION

Epilepsy, a neurological disorder that is characterized by recurrent seizures, affects people regardless of age, sex, ethnicity, or socioeconomic class. The cause of epilepsy in many cases is unknown however some studies have pointed at potential causes including but not limited to genetic mutations and other genetic factors, brain tumour(s), and structural changes in or in areas of the brain due to deformity and/or injury (Singh, Rees, & Sander, 2007). The types of epilepsy that one is diagnosed with - whether it is general, focal, or both - depends on the type(s) of seizures the individual experiences.

Although there is no current cure for epilepsy, there are many treatment options. Nerve stimulation, alternative medicine treatments, herbal and pharmaceutical treatments, diet and lifestyle modifications, and surgery are a few. As a result of the potential side effects of the treatment or combination of treatments chosen, as well as the side effects of seizures, many lives are affected. While new research has shown significant improvement to reduce the negative impact epilepsy has on the afflicted, research has shown promising results that suggest that next step forward in finding a cure, or form of prevention. There is certainly a long way to go before this is accomplished, but humankind has gone a longer way since the initial discovery of the disorder.

BACKGROUND

The discovery of seizures can be traced back to the Babylonian Civilization in 1800 BC (Epilepsy Education Everywhere, 2018.). The Babylonians believed that the seizures were a result of supernatural causes and before it was considered a disorder, people with epilepsy were for a long period of time considered to be demonically possessed, engaged in witchcraft, taking recreational drugs, or even just mentally ill. Since then, the stigma and treatment have

improved significantly due to modern technology and research. However many people who have epilepsy still deal with a stigmas in some communities, side effects from prescribed medication, and must undergo treatment for a long period of time. In 1850 bromides, which are now classified as a first generation antiepileptic drug (AED), were introduced as a treatment of seizures once the the disorder was initially recognized. Bromides are no longer used however, as they have been replaced by more effective medications that have fewer negative side effects (Pearse, 2002).

The powerhouse of the human body, the brain, is made up of millions of nerve cells. These neurons control our thoughts, movements, and feelings by communicating with one another via electrical signals. A seizure comes about when these electrical signals between nerve cells are sent out at too high of a frequency, or are disrupted for any reason (Epilepsy Society, 2013). The brain consists of five different lobes each with different functions including memory, movement, consciousness, general senses, and moods. When the brain undergoes a seizure, depending on where the seizure occurs, different functions of the body are affected. For example, generalized motor seizures (also known as grand mal seizures), which are the most commonly-known type of seizure, affect muscle contractions as opposed to generalized non-motor seizures (also known as absence seizures) where the individual may feel confusion, behave in an unusual manner, or just lose some awareness (ILAE, 2018). Recent studies have shown that genetic mutations leading to epilepsy and epileptic-related conditions can be linked to other conditions such as Autism Spectrum Disorder (ASD) and Alzheimer's Disease (Nascimento et al., 2017). Moreover, because there are some anticonvulsants that are used to bipolar disorder as well - such as Depakote, Lamictal, and Tegretol - inconsistency with medication has proven to show mood instability and there has been evidence to support the link between epilepsy and bipolar disorder (Leo & Narendran, 1999).

CAUSES

A seizure can be defined as the physical findings or changes in behavior that occur after an episode of abnormal electrical activity in the brain. In other words when lots of neurons in the same region of the brain release a burst of abnormal electrical signals a seizure happens (Epilepsy Society, 2013). In order for a seizure to occur, all neurons in that region of the brain must be excited, neurons must be connected to many others within a few synapses, and the message must be large enough to affect the surrounding neurons (Epilepsy Society, 2013). There are few possible causes behind the abnormal activity of neurons in the brain, including neural damage, too many or too few neurotransmitters that might impact interneural communication, slow neural ion channels, etc.

The primary underlying cause for most abnormal neural activity is a result of genetic mutation either during prenatal growth, or later on during childhood and adolescent development. The inheritance of such mutations that contribute to recurrent seizures and thus the disorder is highly complex and relatively under-researched. In fact it is still unknown how the mechanism to stop seizures from happening in the brain works, or whether it even exists. Genetics mutations can either cause neural disorders that result in epilepsy, or may also cause syndrome that affects several parts of the body. Currently there are more than 20 different syndromes with epilepsy as a main feature that have been mapped to specific genes and genetic mutations.

In addition to single-gene epilepsy syndromes the other factors that could contribute to the disorder are metabolic conditions, multifactorial disorders, mitochondrial disorders, chromosomal disorders, and other single-gene disorders than could manifest as epilepsy (Kiriakopoulos, 2018). A less common cause of epilepsy is due to a structural change of the

brain, or areas of the brain. This could be as a result of prenatal, childhood and adolescent growth, head injury, trauma, strokes, radiotherapeutic treatment of tumours in the head region, development of a tumour, etc. Such factors affect and influence the efficiency of neural functions, hence causing recurrent seizures (Singh, Rees & Sander, 2007).

With the advancement of scientific technology and medical research, the underlying causes of epilepsy are in time becoming better understood. Interestingly, the increased focus on epilepsy research in the recent years has proven that there are links between epilepsy and other conditions such as Alzheimer's Disease and ASD (Jeste et al., 2016). In fact a current study that was carried out at the University Hospital in Sweden studied and tested more than 85,000 individuals with epilepsy for ASD as well as their close relatives. The results showed that 1.6% of the individuals with epileptic-related genetic mutations were also diagnosed with ASD, compared to the control group which only had 0.2% of the population diagnosed with ASD (Sundelin et al., 2016). This almost eight-fold difference goes to show that there indeed is a genetic if not anatomical link between the two conditions. The case is similar when looking at the relationship between epilepsy and Alzheimer's, which is made evident in a study that looked at the converging paths of epilepsy and Alzheimer's dementia (Noebels, 2011). According to this study, seizures that occur in the human temporal lobe have a negative impact on cognition and damages of the hippocampal circuitry. This, as a result, leads to progressive memory loss in the long term (Noebels, 2011). Similarly, the toxic accumulation of Aβ peptides as a result of Alzheimer's Disease results in synaptic degeneration, circuit remodeling, and abnormal synchronization within the neural network which could potentially lead to recurrent seizures, or an epileptic-related condition (Jeste et al., 2016).

CLASSIFICATION

According to the Epilepsy Foundation, the International League Against Epilepsy (ILAE) recently revised its classification of seizures to allow for easier diagnosis and classification of seizures (Sirven, 2018). The ILAE, which was founded in 1909, has a mission of improving services and care for epileptic patients as well as promoting research, education and training in regards to the condition (ILAE, 2018).

While initially seizures were divided into two main groups, petit mal and grand mal, the current classification system takes into consideration three main factors: the onset or beginning of seizures, the level of awareness during the seizure, and whether any movements happen during the seizure (ILAE, 2018). Furthermore, other factors are also taken into consideration such as the person's age, their sleep-wake cycle, existence of prior injuries to the brain, genetic influences, if there are medications and/or any substance abuse, what circuits of the brain are involved in the duration of and before a seizure, etc. Figure 1 summarizes the overall classification of seizures in regards to these three main factors, and further categorization according to level of awareness and motor symptoms before and during the seizure.

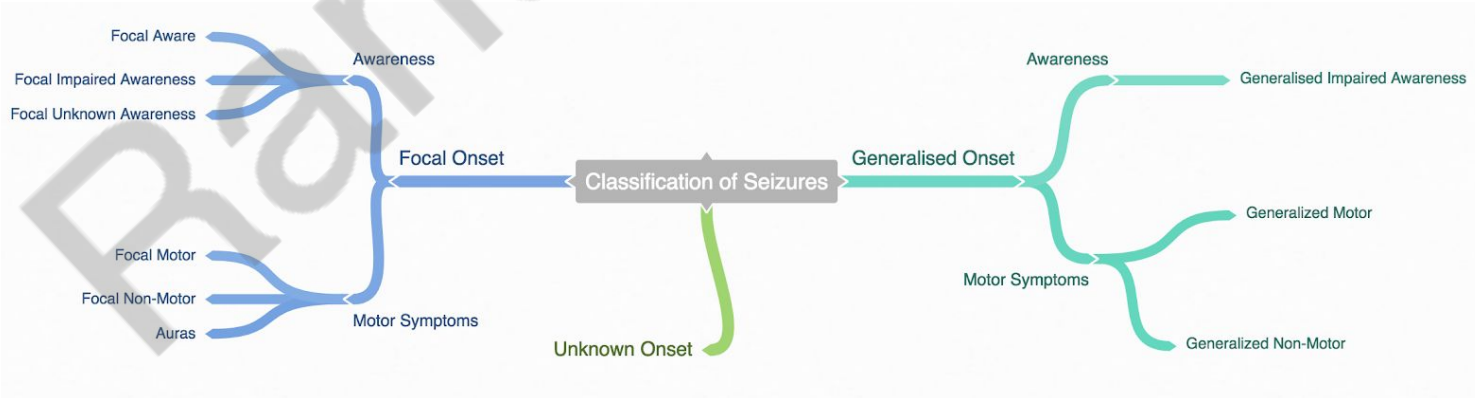

Fig. 1: Adapted flowchart from the ILAE 2017 classification of seizure types (Sirven, 2018)

The first step in classifying seizures is to look at their beginnings - the type of seizure onset plays a significant role in determining what medication to prescribe the patient, as well as whether any surgical procedures or any other form of treatment should be considered. Focal seizures begin in an area on one side of the brain, whereas generalized seizures involve both sides of the brain. If the onset of the seizure is not known it is then classified as an unknown onset seizure, which can be subject to change once the beginning of the individual's seizures becomes clear. Finally, focal to bilateral seizures (previously known as secondary generalized seizures) are seizures that start on one side of the brain and eventually spread to both sides. Table 1 outlines the classification of seizure beginnings and signs to look out for when diagnosing the seizure onset.

Table 1. A summary of the different seizure onset classifications and their respective symptoms, according to the revised 2017 ILAE classification of seizures

Seizure Onset Classification	**Focal Onset Seizure**	**Generalized Onset Seizure**	**Unknown Onset Seizure**	**Focal to Bilateral Onset Seizures**
Previously known as	Partial Seizure	Primary Generalized Seizure	n/a	Secondary Generalized Seizure
Symptoms	- muscle contractions followed by relaxation on just one side of your body. - unusual head or eye movements. - numbness - rapid heart rate or pulse.	- stiff muscles - rhythmic muscle contractions - confusion/arua - pins and needles - Blue skin - Biting lips - Drooling	n/a	- Muscle contraction on one side of body followed by full body contractions - confusion -arua

The second step in classifying seizures is to look at the level of awareness of the individual prior to and during the seizure. Whether a person is awake or not during a seizure is very important as not only does it affect the individual's safety, but awareness is an easier factor to evaluate as opposed to consciousness. Generalized seizures are all presumed to affect a person's awareness so there are no terms to describe level of awareness in this type of seizure (ILAE, 2018). However Focal Onset seizures can be classified in regards to awareness. A Focal Aware seizure is when awareness of the individual remains intact, even if the person is unable to communicate during the seizure. The Focal Awareness Impaired seizure category recognizes seizures whereby awareness is impaired at anytime during the seizure, even if the person has a vague idea of what happened. Finally, Focal Awareness Unknown seizures is used in situations where it isn't possible to know if the person was aware or not, such as if they live alone or only have had seizures at night (ILAE, 2018). Table 2 outlines the classification of seizure awareness levels and signs to look out for when diagnosing the level of awareness during a seizure.

Table 2. A summary of the different classifications of seizure awareness and their respective symptoms, according to the revised 2017 ILAE classification of seizures

Focal Onset Seizure Level of Awareness Classification	**Focal Aware Seizure**	**Focal Awareness Impaired Seizure**	**Focal Awareness Unknown Seizure**
Previously known as	Simple Partial Seizure	Complex Partial Seizure	n/a
Symptoms	Patient is relatively aware of seizure and is able to talk and respond during the seizure	Patient is relatively unaware of seizure and is not able to communicate during the seizure	Patient is unsure if they were able to communicate during seizure due to lack of information

Finally the last step in classifying seizures would be to take into consideration the many other symptoms experienced during a seizure, primarily those that involve movement. For Focal Onset seizures, there are two possible categories for motor-related symptoms that come with the seizure. Focal motor seizures involve some sort of movement during the event, whereas focal non-motor seizures have other non-motor symptoms occur first before any motor movement occurs (ILAE, 2018). Although not a category of focal onset seizures, an aura is a symptom experience by many in the beginning of a seizure whereby a perceptual disturbance is experienced. Generalized onset seizures can also be categorized into generalized motor seizures and generalized non-motor seizures (ILAE, 2018). Table 3 outlines the different motor and non-motor symptoms for both generalized and focal onset seizures. Unknown onset seizures can not be classified in regards to motor symptoms as there is insufficient information due to the unknown beginning symptoms the individual experiences.

Table 3. A summary of the different classifications of motor symptoms before and during a seizure for focal and generalized onset seizures, according to the revised 2017 ILAE classification of seizures

Seizure Onset	**Focal Onset Seizure**		**Generalized Onset Seizure**		**Unknown Onset**
Motor Classification	Focal Motor	Focal Non-Motor	Generalized Motor	Generalized Non-Motor	n/a
Symptoms	Movement occurs during the event; Twitching, jerking, stiffening movements of body part(s).	Other symptoms occur first; Changes in sensation, emotions, thinking, experience(s).	AKA “grand mal”; stiffening (tonic), jerking (clonic)	AKA “absence seizures”; brief changes in awareness, staring, repeated movement.	n/a

Once the three factors of classifying seizures has been done, and the seizures occur in the individual frequently enough to be diagnosed as having an Epilepsy Disorder, further

classification of the type of epilepsy can be done. The different types of epilepsy are General Epilepsy, Focal Epilepsy and both General and Focal Epilepsy. By classifying the type of seizures the individual experiences, whether focal, generalized or both, the type of epilepsy can be determined. Moreover depending on additional factors, the individual could be diagnosed with a specific epilepsy syndrome.

CURRENT TREATMENT

Although a very highly under-researched disorder, there are many current treatments for epilepsy that include pharmaceutical drugs, alternative medicine, lifestyle modification, and surgery amongst other things. The choice of treatment is dependant on the kind of seizures the patient experiences and how frequently they occur, and takes into consideration other general health factors. Although not the most seeked-for and conventional approach to treating the condition, alternative medicine treatments have been used for the longest of times to help treat seizures. Treatments include ingestion of herbs, consumption of food containing certain vitamins (vitamins E, B6, and magnesium), self-control and biofeedback, and acupuncture and chiropractic care (Cherney & McDermott, 2016).

According to a 2003 study of a herbal remedies used in traditional Chinese, Japanese and Indian medicine, some herbs that have been used for thousands of years have shown evidence of their anticonvulsant effects (Tyagi and Delanty, 2003). However there are no randomized nor controlled studies to support these benefits. Alternative approaches are extremely under-researched, and are therefore not as commonly used as modern medicine is because there is little scientific evidence to support these treatments as successful. Of all the alternative medicine approaches the usage of specific dosages of Cannabidiol (CBD) oil has proven to be the most effective in reducing seizure frequency and has, over the years, led to an increased usage of CBD extracts in treating seizure disorders in general - especially in children

(Perucca, 2017). The drawbacks of using CBD oil is that it can get very expensive, and is not legal everywhere so that makes accessibility very difficult.

Although not as effective in controlling seizures, alternative medical approaches result in significantly less side-effects compared to the pharmaceutical approach. Anticonvulsants work by calming hyperactivity in the brain in various ways, and are either used alone (monotherapy) or in combination with other anticonvulsants and/or antipsychotic drugs to control the mania that is often linked with epilepsy (polytherapy). In addition to the side-effects, another disadvantage is that pharmaceutical drugs are significantly more expensive than most alternative medicine treatments (Cherney & McDermott, 2016).

Another treatment approach would be to modify the individual's lifestyle and diet. By reducing factors that have been proven by studies to contribute to lowering the seizure threshold, in some cases medication would not be required to control seizures. A few lifestyle modifications include but are not limited to reducing stress and noise, avoiding flashing lights, ensure adequate sleep and avoid sleep deprivation (especially chronic sleep deprivation), partake in exercise often, and avoid drastic hormonal changes (Cherney & McDermott, 2016). Additionally, adopting the Ketogenic diet, which is a well-known low-carb diet whereby the body relies on production of ketones in the liver for energy, has shown to reduce seizures significantly (Cherney & McDermott, 2016). The drawbacks of lifestyle modification is that it is very risky, and requires consistent monitoring. Service dogs are increasingly popular solution for children and elderly who suffer from chronic seizures. A service dog is one that has been trained to respond to a seizure in someone who has epilepsy and can be trained to alert others when a seizure is coming by barking or activating an alarm, or moving in the way of the person having a seizure to protect them (Brennan, 2018).

The closest thing we have managed to reach to a cure for epilepsy is surgical procedures. Surgery is only considered once the area of the brain where the seizures start, called the seizure focus, has been located and doesn't control a critical function such as language, sensation or movement. There are two main types of surgery associated with epileptic treatment: disconnective surgery and resective surgery. Resective surgery is when the brain tissue is cut away to remove the seizure focus and is most common when the seizure focus is in the temporal lobe (Weiner, Sirven & Shafer, 2013). There are various different types of disconnective surgery, but the most common is the corpus callosotomy. Corpus callosotomy is where the corpus callosum, the band of fibers connecting the two hemispheres of the brain, is cut to prevent communication between the two parts of the brain (Weiner, Sirven & Shafer, 2013).

Although resective surgery is becoming a more popular alternative to treating uncontrollable seizures, not every patient is a good enough candidate for this surgery for a variety of reasons (Uthman, 2000). Therefore nerve stimulation, a new form of adjunctive therapy for epileptic patients, has become more commercially available for uncontrollable epilepsy. There currently exists two types of nerve stimulation for epileptic patients: the non-invasive External Trigeminal Nerve Stimulation (ETNS), and the Vagus Nerve Stimulation (VNS) (Uthman, 2000). The VNS is an add-on treatment for seizures with focal onset both with and without bilateral onset in patients that are at least 12 years of age. The VNS system, made up primarily of a batter generator that delivers the electrical stimuli, is implanted in the left upper chest and connects to the left cervical vagus nerve. Although highly effective, with a seizure reduction rate of up to 20-50%, the VNS is not a cure for epilepsy and anticonvulsant medication will still be taken after the procedure. Additionally, it may take as long as 18 months of VNS before any significant changes take place. However VNS has shown positive results in

shortening recovery time after a seizure and improvements in mood and quality of life in general (Mayo Clinic, 2018).

CONCLUSION

Epilepsy remains one of the most under-researched neurological conditions, yet it is the fourth most common disorder, with 16.5 people per 1000 reporting that they have had epilepsy at some point in their lives (Shafer and Sirven, 2014). Although ILAE releases annual revisions of seizure classification based on research studies as a way to better understand seizures, how they work, and what we could do to reduce and prevent them, we still have a long way before fully understanding the different kinds of seizures and epilepsy syndromes. Figure 2 shows the ILAE 2017 classification of seizure types in detail, whereby the motor symptoms associated with the seizures experiences are in much more depth.

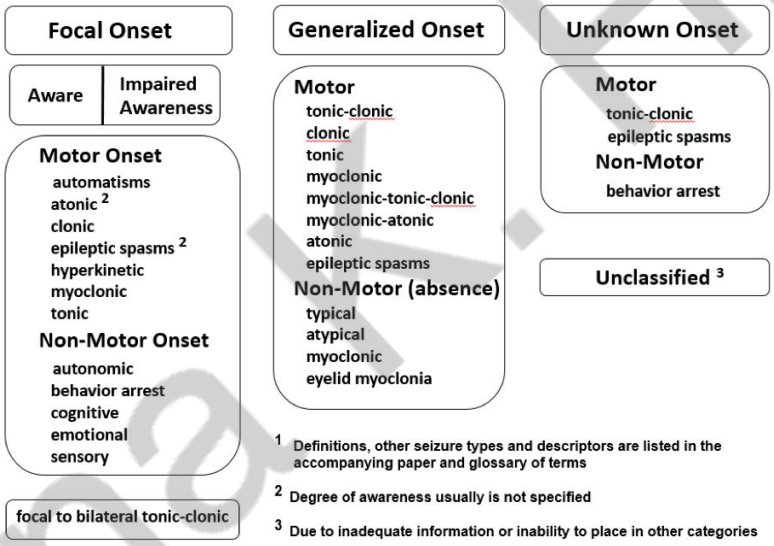

Fig. 2: ILAE 2017 classification of seizure types - detailed version (Sirven, 2018)

Genetic research in the context of epilepsy is becoming increasingly popular with current studies using the novel tool CRISPR - a simple yet powerful tool for editing genomes. This has allowed for better understanding of the genetic causes that lie behind epilepsy, which could potentially point us in the right direction towards finding a cure. One particular study carried out in (Liu et al., 2016) showed evidence that mutations in SCN1A, the gene encoding the α subunit of Nav1.1 channel, can cause epilepsies with a wide range of clinical phenotype. This study

used CRISPR and other genome-editing techniques to induce pluripotent stem cell models to explore the mechanism of epilepsy caused by the SCN1A loss-of-function mutation.

It is with hopes that current and future research will bring light to the condition, allow for more effective treatments and or cure(s) to be established to not only improve the quality of life for those with epilepsy and reduce the side effects of the current treatment options, but also to reduce risk of mortality. Furthermore, with increased research findings we will be able to better understand the link between epilepsy and other linked conditions in order to prevent those with epilepsy from developing such like ASD and Alzheimer's.

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