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Volume 1 • Issue 5 • 2017

Scientia Ricerca

Review Article

Current Opinions in Neurological Science

ISSN: 2575-5447

Epilepsy: A Review

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Received: November 16, 2017; **Published:** November 21, 2017

Abstract

Epilepsy, one of the most common serious neurological disorders, encompasses a group of such disorders. It is characterized by seizures or vigorous shaking that can be brief and nearly undetectable or last for long periods of time. Epileptic seizures have no immediate underlying cause, some occurring as the result of brain pathology (injury, stroke, tumors, infections), genetic mutations, or birth defects through epileptogenesis with a long term risk of recurrent seizures. They are the result of excessive and abnormal nerve cell activity in the brain cortex. Diagnosis of epilepsy is aided (but not necessarily ruled out) by brain imaging and confirmed by an electroencephalogram. Epilepsy that occurs as a result of other issues may be preventable. A substantial fraction of seizures are controllable with medication. In the remaining cases, surgery, neurostimulation, or dietary changes may be considered. Not all cases of epilepsy are lifelong, and many people improve to the point that treatment is no longer needed. Briefly reviewed topics include: the history of epilepsy, its causes and mechanisms. Current treatments are discussed, including: anti=epileptic drugs, surgery, diet and lifestyle modification. Current research in the field is outlined as well as more advanced research options that remain to be pursued. The World Health Organization's fact sheet on epilepsy is provided in an appendix.

Keywords: *Anterior thalamic stimulation; Anti-epileptic drugs; Birth defects; Blood brain barrier; Brain pathology; Chimeric agent receptors therapy; Closed-loop responsive stimulation; Corpus callostomy; Epilepsy; Epilepsy syndromes; Epileptic seizures; Epileptogenesis; Gene therapy; Genetic mutations; Immunotherapy (natural, synthetic, CAR-T); Kindling; Neural networks; Neurological disorders; Neurostimulation; Neuthrophil therapy; Paroxysmal depolarizing shift; Stereotactic surgery; Vagus nerve stimulation*

Abbreviations: AED: Anti-Epileptic Drugs; AS: Angelman syndrome; BRE: Benign Rolandic Epilepsy; CAE: Childhood absence epilepsy: EEG: ElectroEncephaloGram; EE: Epileptic Encephalopathy; ETG: Epilepsy Treatment Gap; MHGAP: Mental Health Gap Action Program; fMRI: Functional Magnetic Resonance Imaging; GABA: Gamma-AminoButyric Acid; GPCR: G-Protein Coupled Receptors; IBE: International Bureau for Epilepsy; ILAE: International League Against Epilepsy; ILEA-CCE: ILEA's Commission for Classification of Epilepsies; JME: Juvenile Myoclonic Epilepsy; LGS: Lennox-Gastaut syndrome; PDS: Paroxysmal Depolarizing Shift; PET: Positron Emission Tomography; WHO: World Health Organization; WS: West syndrome

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Disorders mentioned: Alzheimer's disease; Angelman's syndrome; Arteriovenous malformations; Benign Rolando epilepsy; Brain injury; Celiac disease; Cerebral cavernous malformations; Cerebral malaria; Cerebral palsy; Childhood absence epilepsy; Down Syndrome; Encephalitis (auto-immune); Epilepsy; Epileptic encephalopathy; Head trauma; Infection; Juvenile myoclonic epilepsy; Lennox-Gastaut syndrome; Meningitis; Neurocysticercosis; Non-celiac gluten sensitivity; Parasite infections (with pork tapeworm); Sclerosis (multiple, tuberous); Spastic quadriplegia; Spastic hemiplegia; Stroke; Toxocariasis; Toxoplasmosis; Trauma; Tumor; West syndrome

Drugs listed: Anticonvulsants; Bromide; Carbamazepine; Ethosuximide; Gabapentin; Intravenous immunoglobulins; Lamotrigine; Levetiracetam; Phenobarbitol; Phenytoin; Valporate

Introduction

Epilepsy (in Ancient Greek ἐπιλαμβάνειν, meaning literally to seize, possess, or afflict) is one of the most common serious neurological disorders. It encompasses a group of such disorders characterized by seizures or vigorous shaking that can be brief brief and nearly undetectable or last for long periods of time. Epileptic seizures have no immediate underlying cause, some occurring as the result of brain pathology (injury, stroke, tumors, infections), genetic mutations, or birth defects through a process known as "epileptogenesis" with a long term risk of recurrent seizures depending on the part of the brain affected and on the person's age. They are the result of excessive and abnormal nerve cell activity in the brain cortex.

Diagnosis of epilepsy is aided (but not necessarily ruled out) by brain imaging {functional magnetic resonance imaging (fMRI) and positron emission tomography (PET)), and can be confirmed by an electroencephalogram (EEG). Epilepsy that occurs as a result of other issues may be preventable. Seizures are controllable with medication in about 70% of cases; in the remaining cases, surgery, neurostimulation, or dietary changes may be considered. Not all cases of epilepsy are lifelong, and many people improve to the point that treatment is no longer needed.

As of 2015 about 39 million people have epilepsy (~.80% of cases in the developing world) occurring more commonly in the elderly, which resulted in 125,000 deaths up from 112,000 deaths in 1990. It affects 1% of the population by age 20 and 3% of the population by age 75. It is more common in males than females with a small overall difference. In the developed world, onset of new cases occurs most frequently in babies and the elderly and is more common in older children and young adults, due to differences in the frequency of the underlying causes.

After a brief historical background, the international classification of seizures (whether the original one based on what happens during the seizures or the revised one based on what is their cause) will be summarized. The causes of epilepsies will be addressed whether genetic or acquired as well as the interaction between the two. The mechanisms of seizures and epileptic syndromes will also be reviewed. Current treatments will be discussed including anti-epileptic drugs, surgery, diet and lifestyle modifications. Lastly, research that takes advantage of disruptions in the blood brain barrier, immunotherapy, gene therapy and neutrophils therapy will be outlined.

Historical Background

Epilepsy has affected humanity at least since the beginning of recorded history [1-3]. Throughout ancient history, the disease was thought to be a spiritual possession by evil spirits calling for treatment through spiritual means. It was not until Hippocrates that its explanation was turned from supernatural to naturalistic–a major breakthrough in the history of medicine. Below is a brief history of the disease:

c. 2000 BC: World's oldest description of an epileptic seizure in Akaddian (a language used in ancient Mesopotamia). The person described in the text was diagnosed as being under the influence of a Moon god, and underwent an exorcism.

c. 1790 BC: Epileptic seizures are listed in the Code of Hammurabi as a reason for which a purchased slave may be returned for a refund.

c. 1700 BC: The Edwin Smith Papyrus describes cases of individuals with epileptic convulsions.

1067-1046 BC: Oldest known detailed record of the disease itself is in the Sakikku (a Babylonian cuneiform medical text). It describes signs and symptoms, many features of the different seizure types, treatment details and likely outcomes.

c 900 BC: Unarvasu Atreya described epilepsy as loss of consciousness.

400 BC: The Unarvasu Atreya's definition of epilepsy carried forward into the Ayurvedic text of Charaka Samhita.

400 BC: Epilepsy appears within Greek mythology. One of the names they gave it was the *sacred disease*. It is associated with the Moon goddesses Selene and Artemis, who afflicted those who upset them. The ancient Greeks had contradictory views of the disease. They thought of epilepsy as a form of spiritual possession, but also associated the condition with genius and the divine. Hippocrates rejected the idea that the disease was caused by spirits. In his landmark work "*On the Sacred Disease*" (ἡ ἱερὰ νόσος), he proposed that epilepsy was not divine in origin and instead was a medically treatable problem originating in the brain. He further proposed that heredity was an important cause, described worse outcomes if the disease presents at an early age, and made note of the physical characteristics as well as the social shame associated with it. He called it the "*Great Disease*" (in French: the "*Grand Ma*l").

400 BC-17th century AD: Evil spirits continued to be blamed for the disease.

C 1880-1890: Epileptic patients and the mentally ill were still treated side-by-side at the famous French hospital of La Salpetriere, a foremost institution for neurological diseases.

mid-1880s: Introduction of the first effective anti-seizure medication (*Bromide*).

1912: Development of the first modern treatment of *Phenobarbitol*.

1938: *Phenytoin* came into use.

Classifications of Seizures

There are two classifications of seizures depending on whether the focus is on what happens during a seizure (Table 1) or whether it is on the underlying causes (Table 2):

Classification based on seizure characteristics

Seizure type	Characteristics	Features
1. Generalized: a. Tonic-clonic b. Tonic c. Clonic d. Myoclonic e. Absence f. Atonic	All involve loss of consciousness. Typically happen without warning	1. Contraction of limbs, arching of the back, breathing may stop, etc. Lasts 10-30 seconds. Followed by postictal state 4. Muscle spasms 5. Subtle (right turn of the head, eye blinking) 6. Muscle activity loss (both sides of the body)
2. Convulsive	60% of cases: - 1/3 begin as generalized; may progress to generalized -2/3 begin as focal; may progress to generalized 30% of cases: non-convulsive	Affect both brain hemispheres Affect one hemisphere Example: "absence seizure": decreased consciousness level; usually lasts ~ 10 seconds

3. Focal	Preceded by experiences ("auras"). Jerking activity may start in a specific muscle group and spread to surrounding muscle groups ("Jacksonian march")	Include sensory (visual, hearing, or smell), psychic, autonomic, and motor phenomena
4. Automatisms	Non-consciously-generated,	Repetitive movements (e.g., smacking of the lips) or more complex activities (e.g., attempts to pick-up something)
5. Reflex	6% of cases	Triggered by specific events (flashing lights, sudden noises)

Table 1: *Classification of seizures based on their characteristics.*

Classification based on seizure underlying causes

The International League Against Epilepsy (ILAE) has provided a classification of epilepsies based on their underlying causes (Table 2) and of epileptic syndromes (Table 3) [4-14]:

1. Localization-related epilepsies and syndromes
2. Unknown cause (e.g. benign childhood epilepsy with centro-temporal spikes)
3. Symptomatic/cryptogenic (e.g., temporal lobe epilepsy)
4. Generalized
5. Unknown cause (e.g. childhood absence epilepsy)
6. Cryptogenic or symptomatic (e.g. Lennox-Gastaut syndrome)
7. Symptomatic (e.g. early infantile epileptic encephalopathy with burst suppression)
8. Epilepsies and syndromes undetermined whether focal or generalized with both generalized and focal seizures (e.g. epilepsy with continuous spike-waves during slow wave sleep)
9. Special syndromes (with situation-related seizures)

Table 2a: *Original international classification of seizures based on their underlying causes.*

Following criticisms concerned with the lack of the underlying causes of epilepsy in its classification, the ILEA's Commission for Classification of the Epilepsies (CCE) divided epilepsies into three categories (genetic, structural/metabolic, unknown cause), further refined into four categories and a number of subcategories, reflecting recent technologic and scientific advances (Table 2b):

Seizure type	Causation
1. Genetic	- Unknown (mostly genetic or presumed genetic) - Pure epilepsies due to single gene disorders - Pure epilepsies with complex inheritance - Mostly genetic or developmental - Genetic abnormalities
2. Symptomatic	- Symptomatic (associated with gross anatomic or pathologic abnormalities). May also include some of genetic origin (e.g., Lennox-Gastaut syndrome; Angelman syndrome)

3. Structural/Metabolic	- Mostly genetic or developmental causation - Childhood epilepsy syndromes - Progressive myoclonic epilepsies - Neurocutaneous syndromes - Other neurologic single gene disorders - Disorders of chromosome function - Developmental anomalies of cerebral structure - Mostly acquired causes - Hippocampal sclerosis - Perinatal and infantile causes - Cerebral trauma, tumor or infection - Cerebrovascular disorders - Cerebral immunologic disorders - Degenerative and other neurologic conditions - Provoked (a specific systemic or environmental factor is the predominant cause of the seizures) - Reflex epilepsies - Crytogenic (presumed symptomatic nature in which the cause has not been identified)
4. Unknown cause	60% of cases. Includes some childhood epilepsy syndromes presumed of genetic origin (e.g., benign Rolando epilepsy)

Table 2b: *Revised international classification of seizures based on their underlying causes.*

Causes of Epilepsy

Epilepsy can have both genetic (including congenital and developmental) and acquired causes, with interaction of these factors in many cases. The former are more common among younger people. Established causes for the latter include serious brain trauma (stroke, tumors, infection) and are more likely in older people. Others, known as "acute symptomatic seizures" may also occur as a consequence of other health problems (stroke, head injury, toxic ingestion or metabolic problem). These are included in the broader classification of seizure-related disorders rather than epilepsy itself [15-16].

Genetics

Genetics is believed to be involved in the majority of cases, either directly or indirectly. Some epilepsies due to a single gene defect (1-2%) are rare with more than 200 in all described. Others are due to the interaction of multiple genes and environmental factors. Most genes involved affect ion channels, either directly or indirectly. These include genes for ion channels themselves, enzymes, GABA, and G-protein coupled receptors (GPCR) [16]. Occurrence in the special case of twins is summarized in Table 3:

If both twins are affected, most of the time they have the same epileptic syndrome (70-90%). Other close relatives of a person with epilepsy have a risk five times that of the general population. Between 1 and 10% of those with Down syndrome and 90% of those with Angelman syndrome have epilepsy.

Acquired

Epilepsy may occur as a result of a number of other conditions, as summarized in Table 4 below [17]:

Type of twins	Risk of occurrence
1. Identical twins	- If one twin is affected: 50%-60% chance the other will also be affected - > 50%-60% in generalized rather than focal seizures
2. Non-identical twins	- Risk is 15% - > 15% in generalized rather than focal seizures

Table 3: *Epilepsy occurrence of genetic causes in twins.*

Location or disorder	Risk of occurrence
1.Brain: a. Tumor b. Stroke c. Trauma d. Infection e. Damage at birth f. Cerebral cavernous malformations g. Arteriovenous malformations h. Head trauma i. Brain injury j. High-powered gunshot to the head k. Cerebral malaria l. Toxoplasmosis m. Toxocariasis n. Meningitis o. Herpes simplex encephalitis	a. 30% of cases (or 4% occurrence overall). Greatest for tumors in the temporal lobe and those that grow slowly b. 2%-4% after a stroke f. As high as 40%-60% g. As high as 40%-60% h. 6%-20% i. For mild injury: risk increases two-fold; for severe injury: seven-fold (10). j. ~ 50% 1n. < 10% 1o. ~ 50% for seizure and </~ 50% for epilepsy
2. Neurological disorders: a. Alzheimer's disease b. Multiple sclerosis c. Tuberous sclerosis d. Autoimmune encephalitis e. Cerebral palsy f. Spastic quadriplegia g. Spastic hemiplegia	 f. Increased risk in 50% of people g. Increased risk in 50% of people
3. Celiac disorder: a. Celiac disease b. Non-celiac gluten sensitivity	Not convincing evidence - 1%-6%
4. Parasite infections: a. With pork tapeworm	Can result in neurocysticercosis (~50% in geographical areas affected by the parasite)
5. Chronic alcohol use	2.5X for consumption of 6 units of alcohol per day
6. Malnutrition	Unclear whether a direct cause or an association

Table 4: *Epilepsy occurrence of acquired causes.*

Interactions of genetic and acquired factors

Once regarded as due to demoniacal possession, epilepsies can have both genetic and acquired causes, with interaction of these factors in many cases [18]. To date, nearly all the genes discovered to be involved in human epilepsies encode subunits of ion channels, both voltage-gated and ligand-gated. Ion channels are a common biological substrate for both genetic and acquired epilepsies. Established acquired causes include serious brain trauma, stroke, tumors and infective lesions. Thus, in terms of exploring the neurobiology of 'nature and nurture' in disease, epilepsies are an excellent paradigm.

Mechanisms

Brain electrical activity is regulated by various factors both within the neuron and the cellular environment. It is normally non-synchronous. Factors within the neuron include the type, number and distribution of ion channels, changes to receptors and changes of gene expression. Factors around the neuron include ion concentrations, synaptic plasticity, and regulation of transmitter breakdown by giial cells [19-22].

Epilepsy

The exact mechanism of epilepsy is unknown, although a little is known about its cellular and network mechanisms. It is unknown under which circumstances the brain shifts into the activity of a seizure with its excessive synchronization.

During an epileptic episode, the resistance of excitatory neurons to fire is decreased perhaps due to changes in ion channels or inhibitory neurons not functioning properly. This results in a specific area (known as a "seizure focus") from which seizures may develop. Another mechanism of epilepsy may be the up-regulation of excitatory circuits or down-regulation of inhibitory circuits following a brain injury. These secondary epilepsies occur through processes known as "epileptogenesis". Of importance to our present consideration, may be the failure of the blood brain barrier (BBB) as a causal mechanism as it would allow substances in the blood to enter the brain. This very failure may also allow delivery of therapeutic drugs.

Seizures

Epileptic seizures are usually not a random event; they are often brought on by factors such as stress, alcohol abuse, flickering light, or a lack of sleep, among others. There is a "seizure threshold" that indicates the amount of stimulus necessary to bring about a seizure. This threshold is lowered in epilepsy.

In epileptic seizures a group of neurons begin firing in an abnormal, excessive, and synchronized manner. This results in a wave of depolarization known as a "paroxysmal depolarizing shift" (PDS}. Normally, after an excitatory neuron fires, it becomes more resistant to firing for a period of time.due in part to the effect of one or a combination of three factors: (a) inhibitory neurons, (b) electrical changes within the excitatory neuron, and (c) the negative effects of adenosine.

Focal seizures begin in one hemisphere of the brain whereas generalized seizures begin in both hemispheres. Some types of seizures may change brain structure, while others appear to have little effect. Giiosis, neuronal loss, and atrophy of specific areas of the brain are linked to epilepsy but it is unclear if epilepsy causes these changes or if these changes result in epilepsy.

Epilepsy Syndromes

Cases of epilepsy may be organized into epilepsy syndromes depending on certain specific features that include: the age at which the seizure begun, the seizure type, the EEG findings, etc. Identifying an epilepsy syndrome is useful as it helps determine the underlying causes as well as what anti-seizure medications should be administered. This is more often done with children (Table 5). As discussed earlier, genetics is believed to play an important role in epilepsies by a number of mechanisms. Simple and complex modes of inheritance have been identified for some of them. However, extensive screenings have failed to identify many single gene variants of large effect. More recent exome and genome sequencing studies have begun to reveal a number of *de novo* gene mutations that are

responsible for some epileptic encephalopathies. Classification of epilepsies and particularly of epilepsy syndromes will change with advances in research.

Syndrome	Frequency of occurrence
Benign Rolandic epilepsy (BRE)	2-8/1,000
Childhood absence epilepsy (CAE)	0.8/100,000
Juvenile myoclonic epilepsy (JME)	0.7/100,000
Epileptic encephalopathy (EE)	Frequent seizures resistant to treatment and severe cognitive dysfunction
West syndrome (WS)	
Lennox-Gastaut syndrome (LGS)	
Angelman syndrome (AS)	

Table 5: *Epilepsy syndromes of children.*

Treatment Portfolio

Anti-Epileptic Drugs

Available anti-epileptic drugs (AED), their particulars, effectiveness, adverse effects and recommendations for their use are summarized in Table 6:

Anti-Epileptic Drugs	Particulars	Recommendations
1. Anticonvulsants: - Single agent initially - Second agent helps in ~ 13% - Third agent or two agents combined helps an additional 4%	Mainstay treatment (possibly for entire life). Choice based on: - seizure type, - epilepsy syndrome, - Other medications, - Other health problems - Person's age - Person's lifestyle	~ 30% of people continue to have seizures despite treatment
2. Phenytoin	- Equally effective in both focal and generalized seizures	Controlled release may have fewer side effects
3. Carbamazepine	- Cause increased risk of birth defects	Recommended first treatment line of focal seizures
4. Lamotrigine	Lowest risk of causing birth defects	Recommended second treatment line of focal & generalized seizures
5. Levetiracetam	Lowest risk of causing birth defects	Recommended first treatment line for generalized seizures
6. Valporate	Causes increased risk of birth defects	-Also first treatment line for generalized seizures - Effective in myoclonic and tonic or atonic seizures
7. Gabapentin	Causes increased risk of birth defects	
8. Ethosuximide or valporate		In absence of seizures
9. Phenobarbitol	Causes increased risk of birth defects	Least expensive ($5/year). WHO recommended first treatment line in the developing world

Table 6: *Anti-epileptic drugs, their particulars, adverse effects and recommendations for their use.*

Adverse Effects from Medications

Adverse effects from medications are reported in 10%-90% of people. They cause ~ 25% of people to stop treatment. They are:

- Dose-related: Mild (mood changes, sleepiness, unsteadiness in gait).
- Not dose related: rashes, liver toxicity, suppression of the bone marrow.

Surgery

Surgery, an option for people with focal seizures that remain a problem despite other treatments, includes the following procedures for total control of seizures (achieved in 60%–70% of cases):

- Cutting out the hippocampus via an anterior temporal lobe resection;
- Removing the tumors(s); and
- Removing parts of the neocortex.

For the more limited goal of decreasing the number of seizures, a corpus callostomy may be attempted. Following surgery, medications may be slowly withdrawn in many cases.

Neurostimulation, another option in those who are not candidates for surgery, may include: vagus nerve stimulation, anterior thalamic stimulation, and closed-loop responsive stimulation.

Diet

A ketogenic diet (high fat, low carbohydrate, adequate protein) appears to decrease the number of seizures and eliminate seizures in some people, it is a reasonable option in those who have epilepsy that is not improved with medications and for whom surgery is not an option. Side effects include stomach and intestinal problems (~ 30% of people), and there are long-term concerns about heart disease. Less radical diets are easier to tolerate and may be effective.It is unclear why this diet works and further research is necessary.

In people with celiac disease or non-celiac gluten-free sensitivity and occipital calcifications, a gluten-free diet may decrease the frequency of seizures.

Lifestyle modification

Exercise has been proposed as possibly useful for preventing seizures with some data to support this claim.

Research

Research has proceeded along the following lines [23-26]:

Seizure prediction

Seizure prediction refers to attempts to forecast epileptic seizures based on the EEG before they occur. So far, however, no effective prediction mechanism is known to have been developed.

Kindling

In kindling, repeated exposures to events that could cause seizures eventually cause seizures more easily. This has been used to create animal models of epilepsy.

Gene therapy

Gene therapy is being studied in some types of epilepsy. However, medications that alter the immune function, such as intravenous immunoglobulins, are currently poorly supported by evidence

Non-invasive stereotactic surgery

Non-invasive stereotactic surgery is being compared to standard surgery for certain types of epilepsy. There are no known definitive conclusions.

Neural networks

Common locations for the start of seizures and neural networks have been found to be affected in the majority of epilepsies. Efforts are being deployed to figure out how epilepsy occurs, taking into account the different regions of the brain and the timing of their activity.

New Research Vistas for Acquired Epilepsy

New research vistas may be opened when noting that the blood brain barrier (BBB) may either be disrupted by epilepsy (particularly in the case of acquired seizures) [27-34] or be traversed by synthetic immunotherapy agents [35-40] and neutrophils [41]. These events provide the opportunity for delivering therapeutic drugs more effectively at the brain locations where seizures start, in the right dose, and at the right time. New therapeutic approaches include gene therapy, immunotherapy, whether natural or synthetic using chimeric antigen receptor (CAR) therapy with T- or B-cells, and the as yet undemonstrated applicability of neutrophil therapy to humans. These various subjects will form the subject of companion research articles.

Conclusions

There is an abundant published literature of epilepsy that describes and classifies epileptic seizures, and analyzes the causes of epilepsy as both genetic (including congenital and developmental) and acquired (environmental), with interaction of these factors in many cases. Established causes for the latter include serious brain trauma (stroke, tumors, infection) and are more likely in older people. Others, known as "acute symptomatic seizures" are classified as seizure-related disorders rather than epilepsy. The latter may also occur as a consequence of other health problems stroke, head injury, toxic ingestion or metabolic problem. The mechanisms triggering seizures are sufficiently well known. Regarding treatment, there is a variety of anti-epileptic drugs, some of which extremely inexpensive and more adapted to the needs of the developing world. Other options include surgery, diet change and lifestyle modification. Research in the field has been concentrated on approaches that do not seem to have been very productive so far, including seizure prediction, kindling, gene therapy, non-invasive stereotactic surgery, and neural networks. Fortunately, other research vistas have been identified due to more recent technological and biological advances including taking advantage of the disruption of the blood brain barrier to deliver drugs directly at the source of the seizures, in the right amount and at the right time, immunotherapy (whether natural or synthetic with chimeric antigen receptors and, perhaps, neutrophil therapy if proven applicable to humans).

Appendix

World Health Organization Fact Sheet

For the reader's convenience, the World Health Organization's Fact Sheet on Epilepsy is provided below;

Key Facts

- Epilepsy is a chronic noncommunicable disorder of the brain that affects people of all ages.
- Approximately 50 million people worldwide have epilepsy, making it one of the most common neurological diseases globally.
- Nearly 80% of the people with epilepsy live in low- and middle-income countries.
- People with epilepsy respond to treatment approximately 70% of the time.
- About three fourths of people with epilepsy living in low- and middle- income countries do not get the treatment they need.
- In many parts of the world, people with epilepsy and their families suffer from stigma and discrimination.

Description

Epilepsy is a chronic disorder of the brain that affects people worldwide. It is characterized by recurrent seizures, which are brief episodes of involuntary movement that may involve a part of the body (partial) or the entire body (generalized), and are sometimes accompanied by loss of consciousness and control of bowel or bladder function.

Seizure episodes are a result of excessive electrical discharges in a group of brain cells. Different parts of the brain can be the site of such discharges. Seizures can vary from the briefest lapses of attention or muscle jerks to severe and prolonged convulsions. Seizures can also vary in frequency, from less than 1 per year to several per day.

One seizure does not signify epilepsy (up to 10% of people worldwide have one seizure during their lifetime). Epilepsy is defined as having 2 or more unprovoked seizures. Epilepsy is one of the world's oldest recognized conditions, with written records dating back to 4000 BC. Fear, misunderstanding, discrimination and social stigma have surrounded epilepsy for centuries. This stigma continues in many countries today and can impact on the quality of life for people with the disorder and their families.

Signs and Symptoms

Characteristics of seizures vary and depend on where in the brain the disturbance first starts, and how far it spreads. Temporary symptoms occur, such as loss of awareness or consciousness, and disturbances of movement, sensation (including vision, hearing and taste), mood, or other cognitive functions.

People with seizures tend to have more physical problems (such as fractures and bruising from injuries related to seizures), as well as higher rates of psychological conditions, including anxiety and depression. Similarly, the risk of premature death in people with epilepsy is up to 3 times higher than the general population, with the highest rates found in low- and middle-income countries and rural versus urban areas.

A great proportion of the causes of death related to epilepsy in low- and middle-income countries are potentially preventable, such as falls, drowning, burns and prolonged seizures.

Rates of Disease

Approximately 50 million people currently live with epilepsy worldwide. The estimated proportion of the general population with active epilepsy (i.e. continuing seizures or with the need for treatment) at a given time is between 4 and 10 per 1000 people. However, some studies in low- and middle-income countries suggest that the proportion is much higher, between 7 and 14 per 1000 people.

Globally, an estimated 2.4 million people are diagnosed with epilepsy each year. In high-income countries, annual new cases are between 30 and 50 per 100 000 people in the general population. In low- and middle-income countries, this figure can be up to two times higher. This is likely due to the increased risk of endemic conditions such as malaria or neurocysticercosis; the higher incidence of road traffic injuries; birth-related injuries; and variations in medical infrastructure, availability of preventative health programs and accessible care. Close to 80% of people with epilepsy live in low- and middle-income countries.

Causes

Epilepsy is not contagious. The most common type of epilepsy, which affects 6 out of 10 people with the disorder, is called idiopathic epilepsy and has no identifiable cause.

Epilepsy with a known cause is called secondary epilepsy, or symptomatic epilepsy. The causes of secondary (or symptomatic) epilepsy could be:

- Brain damage from prenatal or perinatal injuries (e.g. a loss of oxygen or trauma during birth, low birth weight),
- Congenital abnormalities or genetic conditions with associated brain malformations,
- Severe head injury,
- Stroke that restricts the amount of oxygen to the brain,
- Infection of the brain such as meningitis, encephalitis, neurocysticercosis,
- Certain genetic syndromes,
- Brain tumor.

Treatment

Epilepsy can be treated easily and affordably with inexpensive daily medication that costs as little as US$ 5 per year. Recent studies in both low- and middle-income countries have shown that up to 70% of children and adults with epilepsy can be successfully treated (i.e. their seizures completely controlled) with anti-epileptic drugs (AEDs). Furthermore, after 2 to 5 years of successful treatment and being seizure-free, drugs can be withdrawn in about 70% of children and 60% of adults without subsequent relapse:

- In low- and middle-income countries, about three fourths of people with epilepsy may not receive the treatment they need. This is called the "treatment gap".
- In many low- and middle-income countries, there is low availability of AEDs. A recent study found the average availability of generic anti-epileptic medicines in the public sector of low- and middle-income countries to be less than 50%. This may act as a barrier to accessing treatment.
- It is possible to diagnose and treat most people with epilepsy at the primary health- care level without the use of sophisticated equipment.
- WHO demonstration projects have indicated that training primary health-care providers to diagnose and treat epilepsy can effectively reduce the epilepsy treatment gap. However, the lack of trained health-care providers can act as a barrier to treatment for people with epilepsy.
- Surgical therapy might be beneficial to patients who respond poorly to drug treatments.

Prevention

Idiopathic epilepsy is not preventable. However, preventive measures can be applied to the known causes of secondary epilepsy:

- Preventing head injury is the most effective way to prevent post-traumatic epilepsy.
- Adequate perinatal care can reduce new cases of epilepsy caused by birth injury.
- The use of drugs and other methods to lower the body temperature of a feverish child can reduce the chance of febrile seizures.
- Central nervous system infections are common causes of epilepsy in tropical areas, where many low- and middle-income countries are concentrated.
- Elimination of parasites in these environments and education on how to avoid infections can be effective ways to reduce epilepsy worldwide, for example those cases due to neurocysticercosis.

Social and Economic Impacts

Epilepsy accounts for 0.6%, of the global burden of disease, a time-based measure that combines years of life lost due to premature mortality and time lived in less than full health. Epilepsy has significant economic implications in terms of health care needs, premature death and lost work productivity.

An Indian study conducted in 1998 calculated that the cost per patient of epilepsy treatment was as high as 88.2% of the country's per capita Gross National Product (GNP), and epilepsy-related costs, which included medical costs, travel, and lost work time, exceeded $2.6 billion/year (2013 USD). (1)

Although the social effects vary from country to country, the discrimination and social stigma that surround epilepsy worldwide are often more difficult to overcome than the seizures themselves. People living with epilepsy can be targets of prejudice. The stigma of the disorder can discourage people from seeking treatment for symptoms, so as to avoid becoming identified with the disorder.

Human Rights

People with epilepsy can experience reduced access to health and life insurance, a withholding of the opportunity to obtain a driving license, and barriers to enter particular occupations, among other limitations. In many countries legislation reflects centuries of misunderstanding about epilepsy. For example:

- In both China and India, epilepsy is commonly viewed as a reason for prohibiting or annulling marriages.
- In the United Kingdom, laws which permitted the annulment of a marriage on the grounds of epilepsy were not amended until 1971.
- In the United States of America, until the 1970s, it was legal to deny people with seizures access to restaurants, theaters, recreational centers and other public buildings.

Legislation based on internationally accepted human rights standards can prevent discrimination and rights violations, improve access to health-care services, and raise the quality of life for people with epilepsy.

WHO Response

WHO and its partners recognize that epilepsy is a major public health concern. As an initiative established in 1997, WHO, the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) are carrying out a global campaign – "Out of the Shadows" – to provide better information and raise awareness about epilepsy and strengthen public and private efforts to improve care and reduce the disorder's impact.

This, as well as other WHO projects on epilepsy, have shown that there are simple, cost-effective ways to treat epilepsy in resource-poor settings, thereby significantly reducing treatment gaps. For example, a project carried out in China resulted in treatment gap reductions of 13% over 1 year and significant improvements in access to care for people with epilepsy.

Projects which aim to reduce the treatment gap and morbidity of people with epilepsy, to train and educate health professionals, to dispel stigma, to identify potential prevention strategies, and to develop models integrating epilepsy control into local health systems are ongoing in many countries.

In particular, the WHO Program on Reducing the Epilepsy Treatment Gap and the Mental Health Gap Action Program (mhGAP) currently seek to achieve these goals in Ghana, Mozambique, Myanmar and Viet Nam. These projects combine several innovative strategies. They focus on expanding the skills of primary care and non-specialist health professionals at the community level to diagnose, treat and follow up people with epilepsy. It will mobilize the community to better support people with epilepsy and their families.

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