Understanding Epilepsy: An Analysis of Pathogenesis, Comorbidities, Treatments, And Potential Research

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Abstract

Epilepsy is a diverse condition that varies in seizure severity, types, and causes. The following scientific literature review provides a comprehensive overview of epilepsy, exploring its various types, causes, and comorbidities. The lack of attention on comorbidities in medical files and in treatment options is also highlighted, as well as the impact on quality of life. The role of genetics in epilepsy research is also explored in the review, including genetic mutations associated with the condition. Genetic mutations have been linked to the development of various types of epilepsy, and recent advances in genetics have allowed for a better understanding of the underlying mechanisms of the disease. However, the identification of unique genetic mutations in the brain remains a challenge, and further research is needed to fully understand their impact. To review, various topics such as diagnosis, drug-resistant epilepsy, and genetics are discussed. The need for a better understanding of comorbidities in individuals with epilepsy, the importance of accurate diagnosis and effective treatment, and the potential impact of genetics on future research is also noted. Finally, the socioeconomic, ethnic, and racial factors are considered when proposing next steps for epilepsy research.

What Is Epilepsy?

Although widely characterized as simply a seizure disorder, epilepsy varies in severity, seizure types, and causes (Sirven, 2015). Epilepsy diagnosis comes with numerous challenges beyond the seizures and other comorbidities that may arise. Accessing high-quality healthcare, coordinating medication management, obtaining vocational and community services, and living with the stigma surrounding neurological disease are all problems that face epileptics (Sirven, 2015). Since 2.2 million people in the United States are said to have epilepsy, along with 65

million people worldwide, (Hirtz et al., 2007) causal factors, comorbidities, treatment options, and inclusivity have become significant in the field of epilepsy research.

In 2014, an International League Against Epilepsy (ILAE) task force refined the definition of epilepsy (Fisher et al., 2005, 2014). According to the ILAE, one is said to have epilepsy when they meet one or more of the following criteria: At least two unprovoked or reflex seizures occurring over 24 hours apart, one unprovoked or reflex seizure and a general recurrence risk of at least 60%, and a diagnosis of an epilepsy syndrome (Sirven, 2015). To convey the seriousness of the condition, epilepsy is now considered a disease rather than a disorder (Sirven, 2015) which speaks to its dangerous potential. Variation occurs, however, in regards to classification, as there are 2 types and 9 subtypes. Consequently, treatments are dependent on whether seizures are of a focal or generalized origin (Sirven, 2015). Focal seizures originate within networks limited to one hemisphere of the brain and can be classified as following, without impairment of consciousness: focal sensory or psychic, focal dyscognitive with impairment of consciousness, and focal evolving to a bilateral convulsive seizure (Sirven, 2015). The terms "simple partial" and "complex partial" have been replaced by "focal without impairment of consciousness" and "focal dyscognitive," respectively (Sirven, 2015). Generalized seizures involve a bilateral hemispheric onset affecting both hemispheres of the brain, and are divided into six categories: tonic–clonic, absence, myoclonic, tonic, clonic, and atonic (Sirven, 2015). Neonatal seizures are no longer considered a separate entity and can be classified within these categories (Sirven, 2015). More specific to focal epilepsy is Sudden Unexpected Death in Epilepsy (SUDEP) (Verducci et al., 2020), which may be due to treatment resistance.

In 2009, the ILAE defined drug-resistant epilepsy as a failure of informative trials of two tolerated and appropriately chosen and used antiepileptic drugs (AEDs), independent of use as a

monotherapy or in combination to achieve a sustained lack of seizures (Kwan et al., 2009). Although AED resistance often indicates the ineffectiveness of future AEDs, medication changes may still lead to improved results in terms of seizures regardless of past AED resistance. Recent studies reported that per year ~5% of patients with intractable epilepsy were seizure free for 1 year following changes in AED (Kwan et al., 2009).

The Genetics Of Epilepsy

For most people with epilepsy, there is no identifiable cause (Perucca et al., 2020). Because of this paradigm, genetics have been brought to the forefront of epilepsy research. In 2018, the ILAE Consortium on Complex Epilepsies published the largest epileptic, genome-wide association study (GWAS) of the time. The research involved 15,212 cases and 29,677 controls, which revealed 16 genome-wide significant loci for epilepsy, of which 11 were not known prior to the 2018 report (ILAE, 2018). Studies identified as GWAS have access to different techniques to analyze DNA sequencing and possible mutations (Perucca et al., 2020). One well proven technique is targeted sequencing, used when researchers are searching for mutations in specific loci known to be associated with epilepsy (Perucca et al., 2020). A second method, Whole-Exome Sequencing (WES), is used when researchers are vying to find novel genes that may be associated with epilepsy. WES examines all the exons in one's DNA, which are the segments of DNA that code for proteins (Perucca et al., 2020). Lastly, Whole-genome sequencing (WGS) is a method used to analyze the entirety of a patient's DNA, assisting in identifying genetic mutations that are not located in protein-coding DNA sequences and identifying new genes that are associated with the disease (Perucca et al., 2020). Notably, de

novo mutation discovery is a specific method that involves the sequencing of parental DNA to identify mutations unique to a child (Perucca et al., 2020).

The execution of the aforementioned methods is also of central importance. Most sequencing is often applied to lymphocyte-derived DNA in the search for pathogenic germline variants (Perucca et al., 2020). Essentially, a patient's DNA, originating in their blood cells, is examined to find germline mutations, mutations that are present in every cell in the body and are inherited from parental DNA. While this method has been proven viable, it may not identify genetic mutations that are only present in the brain, in other words, pathogenic somatic variants (Perucca et al., 2020).

Although the specific variants have yet to be identified, family history data indicate genetic factors play a role in acquired epilepsies caused by a severe head injury or stroke (Perucca et al., 2020). Epilepsy is different from other complex, neurological diseases, such as type 2 diabetes, schizophrenia, and macular degeneration, due to the fact it has a significantly larger number of identifiable Mendelian subtypes in addition to discovered alleles (Perucca et al., 2020). In the context of epilepsy, Mendelian subtypes refer to specific and rare types of epilepsy caused by a single gene mutation or set of mutations (Li et al., 2023). The molecular genetics of epilepsy, however, is dependent on the type of epilepsy with which a patient is diagnosed.
In most cases of Genetic Generalized Epilepsies (GGEs), patients have no immediate family history to suggest epilepsy inheritance, suggesting a polygenic pattern of inheritance, meaning it is the combined effect of multiple genes (Perucca et al., 2020). In one case, heterozygous variants, meaning variation due to two different, inherited alleles of a gene, in the intestinal-cell kinase (ICK) gene can cause juvenile myoclonic epilepsy, and detected ICK variants were deemed to be pathogenic in 22 of 310 cases (7%) (Bailey et al., 2018). Contrastingly, an analysis

of WES data from 1,149 individuals with GGEs and 5,911 ethnically matched controls lacked evidence of rare ICK variants in GGE or juvenile myoclonic epilepsy (Lerche et al., 2019).

While the data argues against disease-causing potential of ICK variants, three deletions - two on chromosome 15 (15q13.3 and 15q11.2) and one on chromosome 16 (16p13.11) - are significant to GGEs since approximately 3% of epilepsy patients carry one or more of these deletions (Mullen et al., 2013). The 15q13.3 deletion encompasses seven genes, including the nicotinic receptor gene (CHRNA7), and has the greatest risk for GGE (95%) (Dibbens et al., 2009). Different from GEEs, focal epilepsies are largely regarded as resulting from an injury to the central nervous system rather than genetics (Perucca et al., 2020). In fact, an increased risk of seizure disorders among relatives of patients with focal epilepsy (1.7–4.4%) is greater than the risk for seizure disorders in the general population (0.5–1%) (Perucca, 2018). Interestingly, the first epilepsy gene to be discovered was in focal epilepsy, a variant in CHRNA4, encoding nicotinic acetylcholine receptor α4 subunit, forming the binding site for the neurotransmitter acetylcholine (Steinlein et al., 1995). In conjunction with genetics, comorbidities also play a significant role in epilepsy as they too are related with the complex genomics behind the neurological disease.

The Comorbidities Of Epilepsy

Comorbidities upon epilepsy diagnosis range from neuropsychiatric disorders to those involving pain (Ottman et al., 2011). A 2008 survey assessed the prevalence of epilepsy and other disorders in the U.S. population (Ottman et al., 2011). To ensure a representative sample, 172,959 respondents aged 18 or older provided information, and to reduce potential bias, the researchers utilized propensity scoring (Ottman et al., 2011) which is a statistical technique

involving assigning a score to each individual based on their characteristics and risk factors for epilepsy, to ensure that the two groups were comparable in their baseline characteristics and health risks (Heinze et al., 2011). The study (Ottman et al., 2011) estimated the PRs of comorbidities in respondents with epilepsy were divided into three categories: neuropsychiatric, pain, and other, which included various conditions such as anxiety, depression, migraine headache, chronic pain, asthma, diabetes, and high blood pressure (Ottman et al., 2011). Two percent (3,488) of respondents reported having been told they had epilepsy or a seizure disorder. Respondents with self-reported epilepsy were more likely ($p < 0.001$) than those without epilepsy to report all six neuropsychiatric disorders (PR from 1.27–2.39), all four pain disorders (PR 1.36–1.96), and asthma (PR 1.25) (Ottman et al., 2011).

Another population survey, focusing on mental health in juvenile epilepsy patients, obtained information by interviewing a caretaker and teacher for a sample size of 10,316 children, including those with epilepsy, diabetes, and those without any known medical condition (Davies et al., 2003). The Development and Well-Being Assessment tool, an interview, parental behavioral reports, and a specialist practitioner rating were used to uncover DSM-IV psychiatric diagnoses for the sample (Davies et al., 2003). The findings from the study highlighted that parents of children with epilepsy consistently reported more problems related to emotional, behavioral, and relationship difficulties than the parents of children with diabetes or no identified medical condition (Davies et al., 2003). These issues had a greater impact on the children, and further regression analyses revealed that epilepsy was independently associated with all the behavioral variables, even when adjusted for age, sex, and severe learning difficulties (Davies et al., 2003).

The aforementioned studies centered around the psychological and physical toll that epilepsy diagnosis could have on adults and children. A problem arises after diagnosis when the focus of a neurologist specialist is achieving seizure control through AEDs, with insufficient attention paid to epilepsy's comorbidities (Suurmeijer et al., 2002). A pilot study found that medical files contained little information regarding these comorbidities, suggesting that medical professionals may not be providing adequate care for psychosocial problems (Suurmeijer et al., 2002). Importantly, the psychosocial comorbidities of epilepsy largely determine how individuals cope with the disease, even after achieving complete seizure control (Boshes et al., 1972).

To gather further knowledge on this treatment and comorbidity gap, researchers selected 210 individuals with epilepsy and gathered information about their health as well as social and psychological functioning through questionnaires and patient files (Suurmeijer et al., 2002). The data was analyzed using hierarchical regression analysis, a statistical technique that examines the predictive value of different variables by adding them to a model in a specific order (Sarstedt et al., 2018). The analysis uncovered the relationship between health perceptions and social and psychological functioning in individuals with epilepsy while considering other factors such as psychosocial status (Sarstedt et al., 2018). Each group of variables (clinical aspects, social functioning, self-efficiency, and psychological functioning, etc.) had a contribution to the quality of life of the study participants (Suurmeijer et al., 2002). The only categories that were omitted due to lack of significance were age and gender (Suurmeijer et al., 2002).

Epilepsy Gene Therapies

Neurodevelopmental comorbidities may be caused by mutations in genes essential to brain development, and are characterized by severe symptoms ranging from intellectual

disability to social or cognitive impairments (Turner et al., 2020). Some of these disorders are closely associated with epilepsy, and share genes associated with neurodevelopmental disorders accompanied by epilepsy (NDD+E) (Turner et al., 2020). NDD+E cases are classified based on their various roles in the brain, such as regulating transcription, intrinsic excitability, and synaptic transmission (Turner et al., 2020). When their function is disrupted, symptoms may appear in the early stages of human life, underscoring the significance of prompt intervention and accurate diagnosis for people with NDD+E (Turner et al., 2020).

Neurodevelopmental disorders with epilepsy are a heterogeneous group frequently caused by de novo mutations in single, protein-coding genes (Turner et al., 2020). Over 100 genes associated with NDD + E have been identified (Turner et al., 2020). One category of genes includes those that alter neuronal activity indirectly by changing other gene regulation (Turner et al., 2020). This gene model is often studied using in vitro methods, such as gene knockdown, and animal model approaches with genetic modifications (Turner et al., 2020). The second category comprises genes that directly change neuronal excitability by targeting ion channels (Turner et al., 2020). Studies on these genes often involve recordings from neurons and animals with genetically modified ion channels (Turner et al., 2020). The third category includes genes that alter synaptic properties, and are studied using both in vitro and in vivo methods, including live imaging of synaptic activity in cultured neurons and in vivo animal models (Turner et al., 2020).

With knowledge of the diverse categories of NDD+E associated genes, delivery vectors must be centralized (Turner et al., 2020). Adeno-associated viruses (AAV) are often employed as delivery vectors due to their advantageous characteristics (Turner et al., 2020). Firstly, AAV have high corporation rates when it comes to genomic integration, or the act of imputing foreign DNA into the genome of a host cell (Turner et al., 2020). Low immunogenicity, or the low chance of a

potentially dangerous immune response or damage to the immune system (Turner et al., 2020) is also beneficial. This in conjunction with natural tissue tropism, the ability for the vector to target specific tissues or organs, make AAV desirable for therapeutic purposes (Turner et al., 2020). AAV9, a variant of AVV, is often utilized for CNS disorders as it displays an affinity for neuronal transduction, the process of introducing DNA into a cell using a vector, and can cross the blood-brain barrier, enabling systemic delivery (Turner et al., 2020). While stereotactic injections, involving the delivery of therapeutic agents to specific locations using a precisely targeted approach based on three-dimensional coordinates, can deliver AAV vectors to specific regions of the brain, systemic routes are less invasive and therefore more favorable for clinical use (Turner et al., 2020).

However, the classification of epilepsy that one has may dictate if one is a good candidate for gene therapy for the treatment of epilepsy (Riban et al., 2009). Approximately 30% of epilepsies are classified as being of genetic origin (Berkovic et al., 2006). Monogenic epilepsies have been identified along with epilepsy caused by multiple genetic mutations in ion channels (Riban et al., 2009). Since then, more than 12 mutations associated with channelopathies, genetic disorders that affect the function of ion channels in the cell membrane, were identified (Berkovic et al., 2006). Pure monogenic epilepsies are rare, and often in complex epilepsies, the impact of environmental influences compared to genetic factors is difficult to assess (Riban et al., 2009).

In 2009, more than a thousand clinical trials using gene therapy were designed, 17 of which targeted neurological diseases such as epilepsy (Riban et al., 2009). The results of phase I to phase III trials are highly promising and indicate that gene therapy does not pose a greater risk than other surgical methods (Riban et al., 2009). Additionally, human testing was conducted on neurological disorders including Alzheimer disease (Tuszynski et al., 2005), late infantile

neuronal ceroid lipofuscinosis (Worgall et al., 2008), Canavan disease (McPhee et al., 2006), and Parkinson's disease (Kaplitt et al., 2007, Fiandaca et al., 2008, Marks et al., 2008) with no significant adverse effects attributed to the gene therapy agent.

Conclusion and Next Steps

Epilepsy is a neurological disorder that affects people of all ages, with the highest incidence rate in children under five years of age and the elderly in North America (Theodore et al., 2006). The overall incidence of epilepsy is approximately 50/100,000 per year, with a prevalence of 5-10/1000, and a standardized mortality ratio (SMR) of 2.3, with evidence suggesting a greater increase in patients with symptomatic epilepsy, particularly children (Theodore et al., 2006). Epileptics are more likely to report reduced quality of life, reduced income, and are less likely to have full-time employment (Theodore et al., 2006). Additionally, stigma is a persistent issue in developed as well as developing countries (Theodore et al., 2006). Because of epilepsy's scope, socioeconomics, gender, ethnicity, and race are all important aspects of epilepsy research moving forward (Theodore et al., 2006).

Several studies have explored the incidence and prevalence of epilepsy in different racial groups in the United States (Theodore et al., 2006). The Oklahoma study found that African-American, Non-Hispanic, and African-American Hispanic populations had a higher incidence of epilepsy compared to white non-Hispanic and white Hispanic populations (Cowan et al., 1989). Additionally, studies from the 1960s and 1990s also found a higher incidence of epilepsy in African-American populations (Haerer et al., 1986, Cowan et al., 1989, CDC, 1994, Murphy et al., 1995) but not all (Kobau et al., 2004). In contrast, a study in Texas found no significant differences in incidence among different racial groups except for Asians, who had a

lower incidence of epilepsy (Theodore et al., 2006). Hence, there are conflicting results regarding the association between race and epileptic seizures (Theodore et al., 2006). Importantly, the prevalence of active epilepsy in various age groups has been documented in different studies across the United States (Theodore et al., 2006). It has been found that the prevalence of epilepsy increases with age and is higher in the elderly population (Theodore et al., 2006).

Due to the aforementioned data regarding ethnicity and race, minorities, including African Americans, Hispanics, and Native Americans, are disproportionately affected by epilepsy compared to the general population (Begley et al., 2000). Despite this, minority participation in clinical research on epilepsy is low, limiting the ability of physicians and researchers to develop effective treatments for these populations (Theodore et al., 2006). Educating physicians on the importance of increasing minority participation in clinical research is the first step toward achieving this societal goal (Stark et al., 2002). Efforts should be made to improve study designs and increase the cultural sensitivity of research protocols (Theodore et al., 2006). Furthermore, it is crucial to address barriers that prevent minority individuals from participating in clinical research studies, including lack of access to transportation and childcare, as well as concerns related to cultural beliefs and traditions (Theodore et al., 2006). Providing solutions to these needs such as childcare and transportation may improve participation rates among minority populations (Snodgrass et al., 2001). In order to reduce inequality in epilepsy care, communities need to reach out to underserved populations more effectively and advocate for cost-effective strategies (Theodore et al., 2006). Collaboration between developed and developing countries can also have educational benefits and provide opportunities to address shared problems with the psychiatric community (Theodore et al., 2006).

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