NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

# The Challenge of Epilepsy

*by*
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## *Rafael*

"Is he going to be alright?" Mrs. Castro asked Dr. Williams. Her 4-year-old boy, Rafael, lay uncomfortably on the bed. Her husband sat on a seat close to his bedside. Rafael's seizure had ended, but Mrs. Castro knew that he would have another one.

Rafael had his first episode two weeks ago. He was playing in the living room when suddenly Mrs. Castro noticed that her son's head was jerking in a peculiar manner. Just as he was about to fall over, Rafael threw his foot forward and regained his balance. His jerking stopped. Mrs. Castro had looked at her son worriedly, but because of the mildness of that first episode, she thought little of it. Perhaps Rafael was just playing.

But another seizure occurred later that week. This time, the jerking was so violent that Rafael fell over with a crash. He lay there on the floor, still moving his head and torso about uncontrollably. Panic seized his mother. She immediately called for an ambulance and notified her husband. The family soon met up at the Hospital for Sick Children in the office of Dr. Lily Williams, a pediatric epileptologist.

"Based on my diagnostic interview, Rafael may have epilepsy," said Dr. Williams.

"Epilepsy?" Mrs. Castro asked, looking slightly bewildered. "But what did we do? What could have caused it?"

"It's too early to say anything yet," the doctor replied. "I am sending Rafael to do an electroencephalography (EEG) test. An EEG is not painful," she added quickly, sensing concern on the mother's face. "A technician will place recording electrodes on your son's head. The electrodes will measure brain activity so we can see how different regions of Raphael's brain are functioning. An EEG is very helpful when someone has had seizures."

"Doctor, could you explain to us a bit more about epilepsy?" asked Mr. Castro, taking his eyes off of his son.

"I was just about to. Epilepsy is a disorder characterized by recurrent seizures like the ones Rafael has had. These usually occur without obvious provocation. What happens during a seizure is that the brain experiences an abnormal, excessive electrical discharge within a population of brain cells, sometimes resulting in jerking muscular motions, as in Rafael's case."

The parents fell silent, pondering the implications of this information. Dr. Williams looked at the family thoughtfully.

"Don't worry for now. There are many things we can do to treat the disorder," she said reassuringly. "Here, I have a brochure that might explain a few things. I will read the EEG recording and send the results to Rafael's pediatrician, and we will go from there."

"Alright. Thank you, doctor," said Mrs. Castro, stowing the brochure into her purse. "We will wait for the results to come out." There was a tremble in her voice. She took Rafael by the hand and left.

## *Different Types of Seizures*

Back at home, Mrs. Castro opened up the brochure that Dr. Williams gave her:

> *[Brochure]*
>
> When people think about seizures, most of the time they think about convulsive seizures. However, there are in fact many different types of seizures that would look entirely different to an outside observer. In fact, some seizures do not cause any observable manifestations at all but may instead result in perceptual changes, mood changes or déjà vu. When someone has experienced two or more unprovoked seizures, a physician would consider epilepsy as a likely diagnosis. The type of seizure is one feature used to characterize the type of epilepsy, which in turn is used to determine the most appropriate anti-seizure drug as well as which other treatment options might be available.
>
> In general, seizures can be categorized into focal and generalized forms. Focal seizures occur when only one part of the brain experiences the discharge that manifest as a clinical seizure.
>
> Generalized seizures begin in both hemispheres of the brain leading to convulsive seizures, myoclonic seizures, absence seizures, or others. As an example, absence seizures cause a loss of consciousness for a few seconds and are often mistaken for daydreaming in children.
>
> A little known fact is that 10% of all people have a seizure at some point during their life. After all, given the enormous complexity of the brain, it is hard to imagine perfect functioning throughout a person's life. What characterizes epilepsy is a risk of recurrent seizures.

Just as she was wondering if Rafael's seizures were generalized or focal, Mrs. Castro's concentration was broken by a call from her husband in the study. "Amanda! Come take a look at this!"

"What is it?" she walked into the study to find Mr. Castro hunched over the computer.

"There's a blog written by someone called Carl who also had epilepsy. Take a look."

> *[ Link: http://carlblogstrom.wordpress.com]*
>
> Many people have asked me about the time in my life when I was struggling with epilepsy. For the benefit of those living with the disorder and also to dispel some myths, I will venture to describe my experiences:
>
> I started having seizures when I was 17. At the beginning of a seizure I had an odd sensation in my abdomen. I could not really describe the sensation to my neurologist at that time but it was something like the feeling you get when an elevator started moving or on a roller coaster. I could not remember what happened next, but my family and girlfriend would tell me that when I had a seizure I did not answer them, had a vacant stare, and often moved my mouth in a chewing motion. This would last for about 3 minutes. I was pretty confused when my seizures ended and it took about 20 minutes or so before I understood where I was and that I had a seizure.
>
> My doctor told me that I had focal dyscognitive seizures. He first prescribed me with a low dosage of Tegretol. But as the seizures continued, my dosage was increased, which controlled them for a short period. But then the seizures became more frequent than before and they appeared resistant to Tegretol at this point. After trying two other anti-seizure medications without success, I was admitted to a specialized epilepsy in-patient unit where they assessed my capacity for surgery.

They did this thing called a video-EEG, and the data from that procedure confirmed that I had focal seizures originating from the right mesial temporal lobe. My doctor told me that my neuropsychological assessment indicated that my left hemisphere was dominant for language and my memory testing indicated some deficits in non-spatial memory functions. That really worried me. But thankfully, because my profile did not indicate a high risk of memory decline or language deficits from a resective surgery, my neurologist and a neurosurgeon suggested I would be a good candidate for epilepsy surgery.

After a right temporal lobectomy, I became seizure-free. A year later I was able to start driving again.

"I've also done a little more research. There's a lot we can do; many options to try," Mr. Castro comforted his wife.

Mrs. Castro sighed. "Well, let's just hope Rafael doesn't need surgery," she said, and went upstairs to tuck Rafael in.

## *Diagnosis and Treatment*

A week later Dr. John Kay, Rafael's pediatrician, received Dr. Williams's EEG report. Dr. Kay diagnosed Rafael with idiopathic generalized epilepsy. "Idiopathic" means that the underlying cause of it is still unknown.

"We don't know for certain the specific type of epilepsy yet. Many types of epilepsy can be well-controlled with medication," Dr. Kay said reassuringly after delivering his diagnosis. "Some can be more difficult to treat. I am prescribing Rafael with a low dosage of EpiVal; we'll see how he responds."

EpiVal is an antiepileptic drug (AED) based on valproic acid. A few months of EpiVal initially appeared to control the seizures, but soon after, the seizures returned. Dr. Kay prescribed a second AED concurrently with EpiVal and gradually discontinued EpiVal. Despite taking the full course of both drugs, Rafael's condition remained stagnant; his seizures would not disappear.

At this point, Dr. Kay diagnosed Rafael with refractory epilepsy, which meant that the seizures did not respond to medication. Based on further descriptions of the episodes and the EEG test, Dr. Kay determined that Rafael had epilepsy with generalized myoclonic-atonic seizures, also known as Doose syndrome.

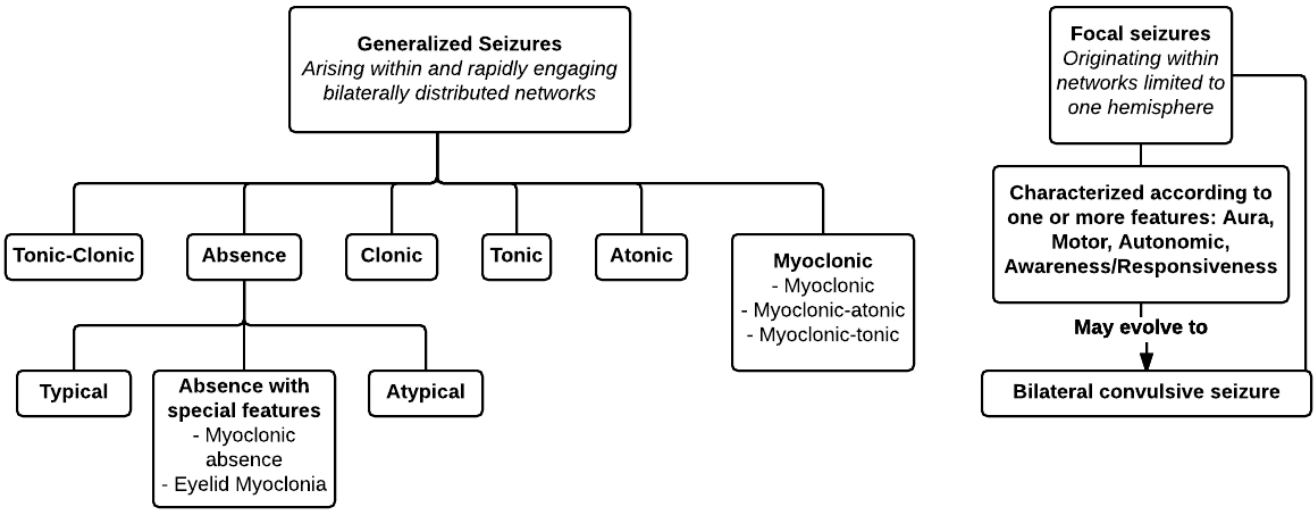


*Figure 1.* A characterization of different types of seizures. Doose syndrome is characterized with myoclonic-atonic seizures under the generalized form. (*Source:* modified from "ILAE Revised Terminology for Organization of Seizures and Epilepsies 2011–2013," <http://www.ilae.org/Visitors/Centre/documents/OrganizationEpilepsy-overview.pdf>, used with permission of ILAE.)

## *Prognosis*

"What do we do now?" Mrs. Castro was back in Dr. Kay's office after the third drug had failed.

"Please don't worry too much, Mrs. Castro. Many cases of childhood epilepsy disappear as the child ages," said Dr. Kay. "In the meantime, I recommend that you record down the times, features and possible triggers each time an episode occurs. Also, there is something else we can try."

"What is it?" asked Mrs. Castro eagerly. She was willing to try anything.

"There is evidence that the ketogenic diet is effective in controlling many cases of refractory epilepsy. The diet involves high fat and low carbohydrates, which makes the body burn fat instead of carbohydrates for energy."

The doctor then gave Mrs. Castro details about this treatment option. "Oh, and one last thing."

"Yes?"

"Try not to make Rafael feel...different. I know you are concerned, and I understand how you must feel as a parent. There may be a necessity to protect Rafael when he is doing certain activities, but please keep in mind that the prognosis for epilepsy is usually pretty good, and most patients are not deterred from leading healthy and fulfilling lives."

"Alright, thank you, Dr. Kay."

"Best of luck."

Dr. Kay sighed as Mrs. Castro left his office. Mrs. Castro's reaction after hearing his diagnoses was surprisingly calm, the doctor thought. Most parents would blame themselves or flare up at the doctor's apparent incompetence. "I had better give this case the best I have," he said to himself. He sat down at his computer and started typing.

## *A Plethora of Research*

*From: JohnKayMD*
*To: JFernandez, ALi, StevePWilson, APatel56*
*Subject: Epilepsy Research?*

Dear Drs.,

I am a pediatrician of a local clinic. Recently I received a patient who is diagnosed with refractory epilepsy. I would like to learn more about the work done in this field. Could you please let me know what sort of epilepsy research goes on in your department and lab?

Yours Sincerely,

John Kay, MD MSc

*From: JFernandez*
*To: JohnKayMD*
*Subject: RE: Epilepsy Research?*

Dear Dr. Kay,

Thank you for your inquiry. The first step to understanding epilepsy is by examining its physiological roots. As you may know, when neurotransmitters are released from neurons, an active reuptake process is necessary to stop the excitation and inhibition of other neurons. Interference with this process has been shown to present or suppress epileptiform activity in animal models.

Of course, it gets a lot more complicated than this. The level of excitability of these neurons is regulated by various mechanisms inside and outside of the neuron and associated cells. It may interest you to look at either of these factors in detail, including the intracellular components and mechanisms of signalling, channels, and receptors, or the extracellular components of synaptic contacts, extracellular ion concentrations, and neurotransmitter metabolism.

It also may be interesting to review Bromfield's "An Introduction to Epilepsy" (found here: http://www.ncbi.nlm.nih.gov/books/NBK2510/) for a general idea of the physiology. Also, check out *Jasper's Basic Mechanisms of the Epilepsies* 4th ed. (found here: http://www.ncbi.nlm.nih.gov/books/NBK50785/) for a detailed collection of physiological research on epilepsy.

Hope this is helpful to your research.

Julian Fernandez
Department of Physiology
University of Toronto

*From: ALi*
*To: JohnKayMD*
*Subject: RE: Epilepsy Research?*

Dear Dr. Kay,

My department delves into the cellular mechanisms underlying epilepsy. Research has shown how some proteins that cross the blood-brain barrier may contribute to the hyperexcitability of the brain, and in other cases, researchers have observed an immunological cause of epilepsy, stemming from antibodies that may impair the brain's functions.

Two cellular mechanisms in particular have been showing increasing popularity in yielding potential targets for drug therapy: the mTOR (mammalian target of rapamycin) signal transduction pathway and the activation of cytokine protein interleukin-1B.

A summary of the research currently going on can be found here: http://www.ninds.nih.gov/disorders/epilepsy/epilepsy_research.htm

Best,

Alan Li
Department of Cell Biology
Western University

*From: StevePWilson*
*To: JohnKayMD*
*Subject: RE: Epilepsy Research?*

Dear Dr. Kay,

There is a category of epilepsy known as idiopathic generalized epilepsy (IGE) whose causation is associated with genetic factors. There has been much research into this area in the past few years and we have found several genes that are related to certain epilepsy syndromes. A key focus has been on genetic mutations that are associated with channelopathies, i.e. when ion channels do not function properly. Recent efforts have expanded towards a larger scale diagnosis of the genome in relation to epilepsy.

Furthermore, it is important not to delve into the mindset of single-gene causation. Indeed, the idea of penetrance stems from the thinking that a disease is caused mostly by one gene. This is often not the case, especially in highly complex cases like epilepsy. I would recommend reading Dr. A. Poduri's "Epilepsy Genetics--Past, Present, and Future" (found here: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4074083/) as well as Greenberg's "Blinders, phenotype, and fashionable genetic analysis: A critical examination of the current state of epilepsy genetic studies" (found here: http://onlinelibrary.wiley.com/doi/10.1111/j.1528-1167.2010.02734.x/full).

Steve Wilson
Clinical and Metabolic Genetics
Hospital for Sick Children

*From: APatel56*
*To: JohnKayMD*
*Subject: RE: Epilepsy Research?*

Dear Dr. Kay,

Different anti-seizure drugs are designed to treat epilepsy patients by working through different pathways. A review paper written by Dr. William Tatum in 2013 summarizes the currently available options. It's entitled "Recent and Emerging Anti-Seizure Drugs: 2013" (http://www.ncbi.nlm.nih.gov/pubmed/23775535). You should take a look there, if you are interested in studying these drugs.

In addition, as you might know, one concern with anti-seizure drugs is the long term side effects. For example, enzyme-inducing drugs such as Phenytoin are associated with an increased risk of osteoporosis . A lot of research is also going into mitigating those side effects. Take a look at "Treatment of Epilepsy to Optimize Bone Health" (http://www.ncbi.nlm.nih.gov/pubmed/21557040).

Besides pharmaceuticals, you may already know about the ketogenic diet. In fact, several neurological disorders including epilepsy can be treated effectively with this diet. We've derived this based on studying the brain structure and behaviour of animal models, but the underlying mechanisms still require elucidation. If you're interested, take a look at "Neuroprotective and disease-modifying effects of the ketogenic diet" (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2367001/).

Hope this helps.

Aaby Patel
Department of Pharmacology and Therapeutics
McGill University

## The Challenge (Version A)

Write a simplified grant proposal for a research idea studying epilepsy.

### *Expectations*

- You may approach your project from a molecular, cellular, physiological, etc., perspective. For example, you may propose to study a specific form of seizure, medication to treat epilepsy, physiology related to the disorder, genetics, etc.
- You may utilize knowledge from several scientific fields including but not limited to biology, chemistry, physics, computer science and mathematics. Interdisciplinary ideas or proposals that are in fields apart from biology are encouraged.
- You do *not* have to explicitly focus on the form of epilepsy mentioned in the case (i.e., Doose Syndrome).
- Your research proposal must be experimental. It cannot be an observational study. It cannot be a clinical survey.
- Your proposal must be for *one* hypothesis (hence one experiment) only.
- You may use diagrams and figures if you believe it aids in your explanation.
- Word limit: 1000 words.

### *Required Contents*

- Abstract (not counted in 1000 word limit)
- Relevant Background Information
  - Any theoretical background related to your specific research area, including specialized vocabulary. (Remember that your judges are scientists, but they may not be epilepsy specialists; you might want to define terms like "tonic-clonic seizure.")
  - Significant experimental progress in your specific research area.
- Aim/Hypothesis.
- Rationale/Significance of Experiment
  - Why is your experiment important to your field of research? How does your experiment relate to your field?
- Methodology
- Definitions Sheet (not counted in 1000 word limit)
- References (not counted in 1000 word limit)

### *Resources*

*Grant Application Guidelines*

http://www.ninds.nih.gov/funding/write_grant_doc.htm#writing

There may not be a hard-and-fast rule in formatting a grant proposal, but not all formats are created equal. This resource is an excellent guide as to what to include and what elements to emphasize in a grant application.

*Sample Grant Application*

http://www.niaid.nih.gov/researchfunding/grant/documents/parrishresplan.pdf

This real-life example of a grant application is slightly different from this case challenge. For one thing, it contains several experimental aims and hypotheses, whereas in this case study you are asked to propose only one.

*Writing an Abstract*

http://www.clinchem.org/content/56/4/521.full

The abstract is the first thing that the judges will see (much like a first impression) and serves as a summary of your proposal.

# The Challenge (Version B)

## *Questions*

1. What is a difference between a seizure and epilepsy?
2. How do neurologists diagnose epilepsy? (What technologies do they use? What do they look for?)
3. What are some limitations in treating epilepsy? (What do we know about epilepsy drugs? Is surgery a panacea?)
4. Read through the email correspondence between Dr. John Kay and the researchers. Pick an area of study that you are interested in. Find a review paper on it and summarize recent findings in your field. You will be graded on the clarity and succinctness of your explanation. (In other words, please do not paraphrase every first sentence of each paragraph.)
5. Propose an experiment related to your area of study. Your experiment must include a hypothesis and methodology. Remember to include appropriate positive and negative controls.