How I learned to stop researching and live in the moment

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"Are you scared?" I asked him. "I don't think about that, there's no point," he replied.

My father: physician, scientist, chief of hematology, member of the National Academy of Medicine, chef, ballroom dancer, wine connoisseur, husband, father, grandfather, sporadic Creutzfeldt-Jakob disease (sCJD) patient, and now Zen master. How do people react when given the diagnosis of a rare terminal illness with zero treatment options? When you come from a family of scientists, the knee-jerk reaction is to delve into the medical literature, to find that elusive detail that informs the hypothesis, and to make sense of the senseless. Indeed, once the initial shock of the diagnosis wore off, I turned to science, not wanting to accept the grim prognosis.

My knowledge of human prion diseases has increased 10-fold in the month since my father received his diagnosis. I learned about CJD subtypes and the highly varied symptomatic presentations of the disease. I read about the promise and subsequent failure of trials of flupirtine, quinacrine, pentosan polysulfate, and doxycycline. I found the mouse trials of antisense oligonucleotides to prevent mRNA from being translated and converted into mutant prion protein. I even looked into how a postdoctoral researcher might acquire some antisense oligonucleotides from the biotechnology company that manufactured the agents used in the mouse research. Sure, I would have to find a neurologist who was willing to inject an experimental drug into my Dad's CSF, but why not? *Anything* seems possible when nothing is possible.

My mother, a biochemist, similarly began furiously researching this horrific disease. That is, after all, what *we* do best. Before the diagnosis, my mother knew of CJD as a protein folding disease that she taught to her medical students in their biochemistry class. Now, it is a reality she faces every day. She initially coped as I did, by turning to science, researching the diagnostic methods involved, and hoping that there was a biochemical possibility of a false positive.

It is hard to feel powerless to help someone you love. It is even harder to accept that that there is no scientific plan, no experimental therapy, and indeed no answer for a disease with such a cruel prognosis. My father dedicated his life to the pursuit of knowledge, becoming a leader and a mentor to many in his field. Then, he contracted this rare, untreatable, and ultimately fatal condition. Anger began to set in. How could science fail him like this? Meanwhile, he continued to go into the office, even as his motor skills continued to fail. I started to bring him his coffee in the mornings because he could no longer carry it himself.

"Don't you want to quit and go… you know… do stuff?" I asked him one morning. "This is what I do," he replied instantly with a smile. I always thought my father would work right up until he couldn't work anymore, I just didn't know it would be so soon.

As I write this, we are currently 4 months from when his first symptoms presented. Five months ago, he was hiking in Peru. Now, he cannot move without a wheelchair. His short-term memory is nearly gone. He is exhausted all the time, can hardly concentrate, and needs help with even the most basic activities of daily life. This all started with mild but progressive ataxia. When the initial tests came back normal—including screening blood work, nerve conduction studies and EMG, and MRI of the brain and spine and EEG—the medical team speculated that the deficits

were secondary to a mysterious autoimmune disease, one that might respond to immunomodulatory therapies. When my Dad continued to decline, despite empiric treatment with IV immunoglobulin, it was hoped that IV methylprednisolone might be the answer. He received only one dose before the results of CSF testing returned from the National Prion Disease Pathology Surveillance Center at Case Western Reserve University.

Known as the RT-QuIC assay for real-time quaking-induced conversion, it detects abnormal prion protein in the CSF of patients. This was the assay my mother had identified during her research as the most specific assay for diagnosing CJD. My Dad's results had come back positive. There could be no question. He had CJD.

My father watched his own father die of Alzheimer disease over a period of nearly a decade. His father before him likely also had symptomatic Alzheimer disease. As for myself, 8 years ago, I developed autoimmune small fiber neuropathy, resulting in my being unable to walk long distances without the assistance of a wheelchair or scooter. And now this. It hardly seemed possible for it all to be unconnected.

As a scientist, I felt that all these puzzle pieces must fit together somehow. As a geneticist, it seemed like it must be written into our DNA. And I had access to our DNA sequences from genetic data, obtained years ago in an attempt to decipher the cause of my own neurologic issues. At that time, my Dad drew our blood in his office and my husband who extracted our DNA. Mom sent it off for sequencing. And my husband and I sifted through the millions of SNPs looking for something that might explain my neurologic/immunologic disease. Some families write folk songs and sing in local talent shows; mine spent their weekends and evenings attempting to unravel the mysteries of obscure neurologic diseases. Ultimately, we could not find any clues to the cause of my own medical problems.

But because we had that data, we knew that my father was homozygous recessive for the M129V SNP in the prion protein (*PRNP*) gene. This explains his particular presentation of sCJD. He has the VV2 subtype, which is relatively uncommon and generally presents with ataxia before cognitive symptoms—exactly what happened with my Dad.

I started to think that if I could not get my father treatment in time, I could at least contribute something to the body of knowledge on prion diseases that would help others in the future. It is known that some proportion of patients diagnosed with symptomatic Alzheimer disease actually have another cause of dementia, such as frontotemporal lobar degeneration, Lewy body disease, or CJD. This makes sense in that there is a continuum of sorts of neurodegeneration, whether it is caused by a buildup of β-amyloid plaques and neurofibrillary tangles, aggregates of tau or alpha-synuclein, or malformed transmissible prions. I wondered whether there was a relationship between the Alzheimer disease that appeared in my ancestors and the M129V SNP in *PRNP*.

In my graduate school days, I worked in a laboratory studying the genetic contributors to Alzheimer disease. Because we still collaborate with them from time to time, I was able to relatively quickly test my hypothesis. I enlisted the help of my husband, a fellow human geneticist. Using a data set of thousands of patients with symptomatic Alzheimer disease, I could detect no association of AD with the M129V SNP, or age at symptomatic onset of dementia, even when controlling for common genetic risks of Alzheimer disease, namely apolipoprotein ε4 carrier status. So much for that hypothesis.

Despair is a difficult emotion to process. What must it be like for a man of science to know exactly, in excruciating detail, what lies ahead with the diagnosis of CJD? This is just one of the many thoughts that I have been obsessing over of late. I know I'm not the only one.

"How are you?" my mother asked him recently. "Okay," he responded. "No, how are *you*?" She, like me, is worried about the psychological toll this illness has to be taking on him. Now much more obviously tired than weeks before when I asked him if he was scared, he still responded with his characteristic wry smile, "You mean the man in the machine?" he asked. "I am resigned to my fate and want to do this gracefully."

This is my father's last lesson for me. If he can still have the mental fortitude to not worry about the things that he cannot change, maybe I too need to close PubMed, put my laboratory notebook aside, and focus on enjoying every moment that I can with him. To make it through by living one day at a time. Even with a brain filling with prions, he is still the smartest person I know.

Acknowledgment

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