What Causes ALS?

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Almost everyone who reads this newsletter has at one time asked the question: "What causes ALS?" I would guess that almost all of you have heard the short version of the answer, which is "we don't know." Those 3 words can be extraordinarily frustrating to individuals with ALS and their families. How can we not know the cause of ALS more than a century after it was first formally described by Charcot, and over 60 years after the death of Lou Gehrig?

The answer is not simply "we don't know," of course. The immediate cause of ALS is motor neuron degeneration. Research has shown that there appear to be many causes of motor neuron degeneration, including glutamate toxicity, oxidative stress, mitochondrial dysfunction, defects of axonal transport, and neuroinflammation. However, we have had trouble answering the most important question our patients ask, which is "why did I develop this condition?" That is where we usually resort to "we don't know." In a small number of cases, ALS is due to a mutation in the superoxide dismutase 1 (SOD1) gene. Over 100 different mutations in this gene can cause a dominantly inherited familial form of ALS. But familial ALS comprises only about 10% of ALS, and of that 10%, only about one-fifth (20%) have an SOD1 gene mutation. Let's do the math: 20% of 10% means that only about 2% of all individuals living with ALS have a clearly identified cause – an SOD1 gene mutation. The other 98% either have familial (inherited) ALS with no identified gene mutation, or have "sporadic" ALS, which means that they do not have affected family members.

A number of other genes have been implicated, but in a less straightforward fashion, including TDP-43, vascular endothelial growth factor (VEGF), hemochromatosis (HFE), paraoxonase, progranulin, and vesicle-associated membrane protein B. The presence of a mutation in one of these genes does not appear to be a direct cause of ALS, as is the case with SOD1, but rather to be associated with an increased incidence (frequency) of ALS. For example, our research and that of others has determined that the presence of a mutation in the HFE gene leads to a significant increase in the probability of developing ALS, but that most people with a mutation in this gene do NOT develop ALS. A similar story describes environmental factors. For example, service in the military is associated with an increased chance of developing ALS, and ALS is now considered a service-connected illness for our veterans. But the vast majority of individual who served in the military will not develop ALS.

So, it is unlikely that gene mutations alone cause ALS in the vast majority of individuals affected. As further evidence against the "genes alone" theory of causation, there are reports of identical twins in whom one develops ALS and the other does not. And, it is equally unlikely that environmental factors alone cause ALS, because many people share an environment with

individuals who develop ALS (spouses, siblings, neighbors, other servicemen and women), yet most do not develop ALS. So, if genes or environment alone do not cause ALS, what does cause ALS? Many physicians and scientists in the ALS community now believe that individuals develop ALS because of a combination of a genetic predisposition and environmental triggers. This theory holds that a combination of specific genes increases the probability of developing ALS, and that some trigger, perhaps an environmental toxin, or something in one's food, for example, then produces ALS when a specific gene combination is present. There may be many different genes and gene combinations that increase the probability of developing ALS, and many different environmental triggers as well.

Based on this way of thinking, ALS is not a disease, but rather a syndrome. That is, we as physicians see only the end result – the loss of motor neurons – but not the reason for it. This is similar to the way physicians in the past looked at congestive heart failure. The term congestive heart failure simply describes the end result, which is a heart which pumps the blood poorly and inefficiently, leading to fluid accumulation (edema), poor exercise capacity, and other limitations. But, congestive heart failure may have many causes, including valvular hear disease, coronary artery disease, or a virus producing enlargement of the heart (cardiomyopathy). Unless we know the cause or causes of the heart failure, our understanding of the condition and our ability to treat are limited. As an extension of this way of thinking, our ability to treat ALS is limited because of our lack of insight into the cause in any particular individual. Better treatments will depend on an ability to identify the cause in a particular individual, or on a therapy which can directly address the loss of motor neurons, such as perhaps stem cell therapy.

I am hopeful that over the next few years we will be able to screen individuals with ALS for a variety of different gene mutations to determine why they were predisposed to develop ALS, and I am also hopeful that ALS registries and ongoing epidemiological studies will help identify common environmental triggers. If such advances are made, the term ALS eventually will be only a general description, and we will be able to classify the condition much more precisely in individuals, based on genetic and environmental factors. Hopefully this will permit specific treatments aimed at the underlying causes in specific individuals. In the meantime, treatments will continue to be directed toward slowing progression and prolonging lifespan, combined with the best possible supportive care. That is the current goal of ALS Centers, chapters, and all of us involved in the care of individuals with this condition.