Ask the Neurologist:
Challenges in Designing Treatments for ALS

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The questions in this newsletter will focus on some of the challenges in designing treatments for ALS.

How are drugs determined to be of value for treating ALS?

Many mechanisms have been proposed as the cause of ALS, including glutamate toxicity, oxidative stress, neurofilament dysfunction, mitochondrial dysfunction, and protein misfolding, among others. Treatments are based on these mechanisms. For example, Riluzole (Rilutek) is an anti-glutamate drug. Various vitamins and other natural compounds that we recommend are anti-oxidants (to combat oxidative stress). New compounds are being designed to address the other potential causes listed here, as well as a variety of others. There are many ways that research studies in the laboratory can determine whether certain compounds may be of value in altering the mechanisms thought to lead to motor neuron death in ALS. If a compound shows promise, it is then tried in an animal model, typically the SOD1 mouse model of ALS.

What is the ALS mouse? Do mice get ALS?

Mice do not normally develop ALS. The "ALS mouse" is a transgenic mouse, into whose DNA a mutated human gene is inserted. This SOD1 mutation causes the mouse to develop a motor neuron disease in a predictable fashion as the mouse ages. By treating the mouse with a drug which shows promise for improving motor neuron survival, it is hoped that the drug will either prevent the development of motor neuron degeneration in the mouse, delay the time of motor neuron degeneration to a later stage in the mouse's life, or slow the rate of motor neuron loss once that loss begins.

How good has the mouse model been at predicting drugs that will work in ALS?

Unfortunately not very good. Many compounds have shown promise in the mouse model, only to be unsuccessful in humans. Recently, this has included creatine, topiramate, and celecoxib (Celebrex).

Why isn't the mouse model a more successful predictor of success in humans?

Part of the reason is the way that the experiments are done. The mice are often treated with the drug before they begin to develop signs of motor neuron disease. In humans, of course, we can treat only once the illness has begin. And, it is estimated that by the time a person notices weakness from ALS, he or she has lost 50% of the motor neurons supplying that muscle group! Another reason for the lack of success in humans probably has to do with the differences between SOD1-associated ALS and the sporadic form of ALS that occurs in most people with the disease. Only about 5-10% of people with ALS have familial (genetic) ALS, and of that small group, only about 20% have an SOD1 mutation. Thus, only about 1-2% of all people who have ALS have an SOD1 mutation as the cause. Yet, we use the SOD1 mouse as the model to test these drugs because, unfortunately, we do not have another animal model of ALS. Also, mice may break down the drug differently than we do, and therefore have very different levels of the drug circulating in their bodies when given a particular dose. Importantly, we rarely know what the concentration of the drug is in the central nervous system (CNS, consisting of brain and spinal cord). The CNS is protected by the blood-brain barrier, which is designed to prevent toxins from entering our brain and spinal cord. The consequence of this is that it is very difficult to get drugs through the blood-brain barrier and into the CNS, where it is needed if it is going to be effective to treat ALS. So, it's possible that some of these drugs that show promise in mice are not being given to people in the doses needed to penetrate into the CNS in sufficient quantities to be effective. One area of active research in ALS is the study of better mechanisms of drug delivery across the blood-brain barrier.

We test drugs for effectiveness in all ALS patients, yet ALS has many different clinical presentations. Does ALS have the same cause in every person affected by the disease?

Unfortunately, we do not know. ALS has a wide variety of clinical presentations. It may be primarily bulbar or limb; the individual affected may be in his or her 20s or 80s (or anywhere in between); the course may be very rapid or very slow, proceeding from onset of symptoms to death in less than one year or more than 10 years. It is entirely possible that there may be many different forms of ALS, each of which has one primary cause, or there may be multiple causes of ALS which combine in unique ways in each individual who develops the disease. Perhaps in the future, we will classify patients as having ALS type 1, type 2, type 3, etc, and direct our treatment specifically to the type of ALS they have, based on knowledge of the cause of each specific type. But, currently, we try new drugs for ALS as if it is a single disease. In contrast to this experimental approach, most individuals affected by the disease try a more diversified approach, taking Riluzole plus anti-oxidant vitamins plus often a new or experimental treatment. In a similar manner some investigators recommend a "cocktail" approach to treat ALS, in which a combination of drugs is used, each of which targets a different possible cause of the disease. That is why basic research into the causes of ALS is so important. When we understand the underlying mechanism of ALS in each individual affected, our methods of determining the best treatment will be individualized and thus much more effective.