Developing a biomarker for a neurological disease such as ALS is a long and challenging process, according to Andreas Jeromin, Ph.D., who spoke in a recent webinar sponsored by The ALS Association. He said, however, they are highly useful tools for improving diagnosis, understanding and predicting a patient’s prognosis, and perhaps especially for speeding clinical trials. For those reasons, finding a reliable biomarker in ALS is a top priority for The Association and for researchers in the field.

A biomarker is a substance or process that can be measured and can provide information about the disease state. A classic example of a biomarker is found in the cardiology field. After a heart attack, a protein called troponin is released from the damaged heart muscle into the bloodstream, in a time-dependent way. Doctors can use the level of troponin to gauge not only that a patient has had a heart attack, but also how long ago it occurred and how severe it was.

Dr. Jeromin, who is Chief Scientific Officer of NextGen Sciences, is helping to develop biomarkers for Alzheimer’s disease, based on changes that can be seen in images of the brain. Lucie Bruijn, Ph.D., Chief Scientific Officer for The ALS Association, who hosted the webinar, pointed out that neuroimaging is widely used in the multiple sclerosis (MS) field, where, along with improving diagnosis, it has greatly sped the discovery of new drugs.

“These imaging biomarkers have increased the interest of pharmaceutical companies in drug development for MS,” Dr. Bruijn said. In MS, the symptoms of disease fluctuate over time, and discerning progression against that background is difficult. Imaging helps remove the uncertainty, reducing the time and patient numbers needed to test a drug.

Similarly in ALS, she continued, current trials depend on measuring survival or changes in the ALS Functional Rating Score, both of which mean clinical trials need to be many months or years long, slowing drug development. Having a biomarker that could be measured quickly to determine if the drug were having an effect would speed trials.

For ALS, one of the most promising biomarkers is a protein called phosphorylated neurofilament heavy chain (pNFH). This protein is part of the “cytoskeleton” used by cells, including motor neurons, as an internal support system. As neurons degenerate, pNFH is released from the cells into the fluid that surrounds the brain and spinal cord, called cerebrospinal fluid (CSF). The level of pNFH in the CSF is higher in ALS patients than in healthy control individuals and is also higher than in patients with Alzheimer’s disease, indicating it is probably a specific marker for ALS.
The pNFH protein becomes an even better ALS biomarker when combined with another protein also found in CSF, called complement C3. The complement system is part of the body’s immune system. A high ratio of pNFH to C3 is a highly predictive marker for the presence of ALS. Recent testing indicates it correctly distinguishes an ALS sample from a control sample more than 90% of the time.

“This test has also been adapted to use a sample from blood, with very encouraging results as a marker for diagnosis and for disease progression,” Dr. Jeromin said, since the ratio changes over time. It is also potentially a therapeutic response marker, since if the underlying neurodegenerative process is slowed by treatment; it should be reflected in a change in the level of proteins released by motor neurons.

Dr. Bruijn pointed out that the development of the pNFH/C3 test is a good example of the collaborative nature of ALS research, as it began with researchers working in animal models and very quickly moved to validation in the clinic by other scientists.

Other biomarkers are also being explored, Dr. Jeromin said, with results expected to be made public in the near future.

Dr. Bruijn emphasized the importance of patient participation in clinical biomarker research. “We can put you in contact with those studies in your local area,” she said, or even at centers far from home, since often the study can be done with blood or CSF samples that can be collected near home and then sent to the study center.

To learn more about biomarker studies for ALS, go to www.clinicaltrials.gov and search for “amyotrophic lateral sclerosis biomarkers,” or follow this link: http://www.clinicaltrials.gov/ct2/results?term=amyotrophic+lateral+sclerosis+biomarkers&Search=Search

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