Imaging Inflammation in the Brain May Speed Development of New Treatments

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Speaker: Nazem Atassi, M.D., Massachusetts General Hospital
Host: ALS Association Chief Scientist Lucie Bruijn, Ph.D., M.B.A.

By Richard Robinson

Within the past decade, inflammation has emerged as a major contributor to the disease process once ALS has begun, which makes it a key target for slowing disease progression and a key focus of biomarker development. Developing such biomarkers is the focus of research by Nazem Atassi, M.D., Program Director at the Neurological Clinical Research Institute at Massachusetts General Hospital and Assistant Professor of Neurology at Harvard Medical School. Dr. Atassi outlined that research in a webinar, hosted by ALS Association Chief Scientist Lucie Bruijn, Ph.D., M.B.A.

Inflammation is an immune system defense program that comes into play when tissue is damaged. Outside the central nervous system, it is characterized by redness, tenderness, and swelling, as chemicals and immune cells converge to clean up the damage. Inside the central nervous system, there is no swelling or pain, but cells still move to the damaged area, where, paradoxically, they appear to worsen the damage by harming neurons.

Experiments in ALS animal models show that reducing inflammation after disease onset can slow disease progression, suggesting the potential for therapies that could be effective at prolonging function and survival. “It is slowing down the disease after it starts,” Dr. Atassi said. “This is important because we see the person with ALS only after their disease begins. So this is very relevant to drug discovery.”

In people with ALS, inflammation within the brain can be imaged using tracers, molecules that bind to pro-inflammatory cells. In work funded by The ALS Association, Dr. Atassi and colleagues have developed and begun testing a tracer that binds to a protein on the surface of immune cells known as astrocytes and microglia. Tracer can be detected using PET imaging, in which the subject lies in a combination MRI and PET scanner. The MRI image provides a highly-detailed map of the brain, onto which Dr. Atassi overlays the location and intensity of the tracer. “It sounds like science fiction, but it’s a reality,” he said.

In a pilot study, Dr. Atassi has shown that a tracer can show the degree of neuroinflammation in the brain of people with ALS. These initial studies showed that the most severe inflammation was found in the brain region (motor cortex versus brainstem) controlling the most severely affected body region (limbs versus bulbar muscles). In addition, an overall higher degree of inflammation correlated with worse physical functioning.
“This was a small study,” he cautioned, “and we have a chicken-and-egg problem: does the inflammation cause the worsening, or does the worsening cause the inflammation?”

To address that question, Dr. Atassi is beginning a longitudinal study of more people with ALS, co-funded by The ALS Association and ALS Finding a Cure. The study is part of the ALS ACT program, a major new initiative funded in part by The Association, and is drawing on imaging expertise from GE Healthcare. Multiple scans in the same person, over time, should be able to determine whether inflammation is contributing to disease worsening.

“The development of this system could help us do very efficient clinical trials,” Dr. Atassi stressed, since it would both track disease progression and response to anti-inflammatory therapy; several such agents are being studied in ALS. Without a good biomarker, he said, a trial would require more than 500 people with ALS and last more than a year. The time and cost means, “We can’t test every drug we want to test.”

But with a biomarker such as this, trials can be smaller and faster allowing evaluation of many more drugs, with the most promising rapidly advancing to larger, definitive trials. An inflammation biomarker could also promote “personalized medicine,” in which the choice of drug is tailored to the person’s specific disease process. Inflammation may be very important in some people but not in others, Dr. Atassi added.

“This is very exciting work,” said Dr. Bruijn. “We are eagerly awaiting the further analysis of this imaging system to determine its potential for speeding up testing of new treatments and learning more about the contribution of inflammation to the disease process.”

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