



Discoveries Give New Meaning to “Familial” and “Sporadic” ALS

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Host: ALS Association Chief Scientist Lucie Bruijn, Ph.D.

Guest Speaker: Michael Benatar, M.D.

When it comes to understanding the genetic causes of ALS, the pace of discovery has quickened significantly in recent years. These discoveries have caused ALS researchers to rethink the meaning of the terms “familial” and “sporadic” disease, according to Michael Benatar, M.D., of the University of Miami’s Miller School of Medicine. Dr. Benatar spoke in a recent webinar sponsored by The ALS Association, hosted by Chief Scientist Lucie Bruijn, Ph.D.

Until recently, there was a clear distinction between familial and sporadic disease. Familial referred to cases in which at least two family members had ALS, while sporadic referred to single cases with no other family members involved. Genes were thought to underlie familial cases, but not most sporadic ones.

New discoveries, especially the C9ORF72 gene, “are causing us to rethink our definitions,” Dr. Benatar said. “One of the things we realized is that sometimes some of the people who have sporadic ALS can have a genetic cause.”

In some apparently sporadic cases, probing more deeply in the family history may reveal a relative who also had ALS, or perhaps the form of dementia known as frontotemporal dementia, which can also be caused by the C9ORF72 gene. “In deciding whether a disease is sporadic or familial, it is critical to take a full family history,” he said.

While known genes account for 60% of familial disease, the cause of a full 40% of familial cases is still unknown. This is an active area of research, and one in which Dr. Benatar is deeply involved in. “We also don’t know why some people with a gene mutation develop ALS and some people don’t. And we don’t know why there is such variability in age of onset, even among people with the same genetic abnormality. Understanding this is an important area of research,” since understanding more about factors that influence when the disease begins may provide clues about how to delay onset or slow progression.

Researchers are also trying to determine how each of the known genes leads to motor neuron disease. As new genes are discovered, they provide new insights into the multiple proposed mechanisms for the disease, including oxidative stress, excitotoxicity, RNA processing defects, mitochondrial dysfunction, protein aggregation, and prion-like mechanisms that spread misfolded proteins from one cell to another. It is not yet clear whether all ALS patients would respond to a single treatment strategy, or whether disease caused by different genes will require different therapeutic interventions.

Neuroimaging may help answer one of the most pressing questions in familial ALS research: When does the disease begin? “Presymptomatic” disease is the term to describe the phase before overt symptoms are seen in a person who will develop ALS. Dr. Benatar is using magnetic resonance imaging (MRI) of the brain and spinal cord to compare people with presymptomatic and symptomatic ALS, to see if there are similarities that unite them and distinguish them from those without ALS. Early results suggest there are such similarities.

“We hope we can use this knowledge to design an early preventive clinical trial,” Dr. Benatar said. It is also hoped that neuroimaging changes may be used more broadly as a biomarker for ALS progression and response to therapy. Dr. Bruijn noted that Dr. Benatar has been a pioneer in this field, especially in developing ways to image the spinal cord.

Several trials in familial ALS are currently under way. These include:

- Arimoclomol, which is completing a Phase II safety trial, with plans to go on to a Phase III efficacy trial if the drug proves safe;
- Pyrimethamine, originally an antimalarial drug, meant to lower SOD1 protein, in an open-label Phase I safety trial;
- SOD1 antisense therapy, which recently completed a small safety trial with no safety concerns.

“Progress has been made” in understanding the genetics of ALS, Dr. Benatar concluded. “I think therapies will follow, although these will take time. It is crucially important to have a partnership between scientists and the familial ALS community. This work cannot be done without your participation.”

“The contributions of familial ALS patients and families to ALS research is critically important,” said Dr. Bruijn, “and becomes even more so as we learn more about the complex genetics of the disease. I would like to echo what Dr. Benatar said: we need your help.”

Several resources for familial ALS are available, in addition to those provided by the ALS Association: <http://als-research.org>, which is the project led by Dr. Benatar to understand familial ALS, and <https://fals.patientcrossroads.org/> is a familial registry whose goal is to help connect familial ALS families with researchers.

To view the entire webinar, visit:

<https://alsa.webex.com/alsa/ldr.php?AT=pb&SP=MC&rID=65556157&rKey=f518bb402345d1f2>