What MRI Can Do for Ataxias and Why More MRI Research is Needed

By Gülin Öz, PhD

Center for Magnetic Resonance Research, Department of Radiology, University of Minnesota, Minneapolis, MN

The brain, or “the three pounds of matter that sits between our ears” as President Obama described it, is unlike any other organ: a complex network of more than 80 billion neurons encased in the skull, surrounded by cerebrospinal fluid and protected by the blood-brain barrier from potentially hazardous chemicals in the circulation. Highly protected and not easily accessible…

Ataxias affect the cerebellum (the “little brain”) that takes up only 10% of the total brain volume but contains more neurons than the rest of the brain put together. This little brain controls our movements, including our gaze, speech, gait and balance. As in all other neurodegenerative diseases, it is a major challenge to access and monitor the underlying brain pathology in ataxias. Dysfunction and loss of the neurons in the cerebellum cause the balance and coordination problems that can easily be assessed and monitored by a clinical examination, but clinical symptoms do not tell the whole story. Scientists now know that the changes in the brain in neurodegenerative diseases start years before symptoms occur. That is, neurons are struggling long before they die. Using mouse models, researchers demonstrated that neuronal dysfunction is reversible and this ‘dysfunction’ period would be the time for application of neuroprotective therapies — to delay the onset of symptoms and slow the progression of the disease; to help the struggling neurons. Tools to detect these early changes and to monitor the progression and perhaps even the slowing down / reversal of pathology by novel drugs directly in the brain have been limited. In addition, drugs that improve symptoms such as the balance problems in ataxias, do not always slow the progression of the brain pathology. Therefore tools that can distinguish such symptomatic effects from ‘disease-modifying’ effects of drugs are highly desirable. That is where non-invasive neuroimaging technologies such as magnetic resonance imaging (MRI) come in.

MRI technology uses radio frequency pulses and strong magnetic fields to allow non-invasive access to brain structure and function. It does not involve radioactivity (“ionizing radiation”) and therefore serial scanning does not present a concern. There are many ways to use the MRI scanner to obtain different and complementary information about the brain. MRI techniques most commonly measure the water in the body (the brain is made up of 70-80% water), but other brain chemicals (neurochemicals) can also be detected and quantified by a specialized MRI modality called MR spectroscopy (MRS). Clinical MRI scanners typically have a magnetic field strength of 1.5 tesla (T), but high (3T) and ultra-high (7T) field scanners provide even higher sensitivity, better images and more reliable structural and functional information on the brain — which is why many academic hospitals are now also using 3T scanners.
MRI is currently used in the clinical care of ataxias as a diagnostic aid, to detect the atrophy (shrinkage) of the cerebellum. But this is only the most basic information that the MRI scanner can provide on brain anatomy. Using different MRI techniques we learn about the connectivity and wiring in the brain (diffusion MRI), brain chemistry (MRS) and blood flow and function (functional MRI) among others. All of these various MRI techniques have been used to study ataxias. For example, using structural MRI, researchers have observed different patterns of brain atrophy in different ataxias and that the brain tissue loss reflects disease severity. Others have shown that disruptions in the brain connectivity in ataxias can be detected using diffusion MRI. Chemical changes that occur with disease progression can be detected by MRS and they reflect the severity of cerebellar pathology.

The potential for all this new information to one day affect clinical decision making is great, but there is much more to do. These new technologies, which can one day help with differential diagnosis in ataxias (e.g. which genetic test to perform first when a family history is not available), with monitoring drug effects in clinical trials and with understanding disease processes so that novel treatments can be devised, need to be tested and validated thoroughly for the many ataxia subtypes before they can be used in the ataxia clinic – which is why continued support for this research by the National Institutes of Health (NIH) and other organizations is critical.

Unfortunately when it comes to NIH funding, we are currently in a pickle. The economic struggles of the last decade are also felt strongly in the research environment. The NIH receives more and more grant applications, most of which cannot be funded as NIH’s purchasing power has been reduced by 20% over the last 20 years due to flat budgets.

In this tough environment with waning support for biomedical research, the new Brain Initiative (Brain Research through Advancing Innovative Neurotechnologies, [www.whitehouse.gov/infographics/brain-initiative](http://www.whitehouse.gov/infographics/brain-initiative)) is most welcome and expected to provide some support for MRI research. The Initiative is launching with $100 million in funding for research supported by the NIH, the Defense Advanced Research Projects Agency (DARPA), and the National Science Foundation (NSF), pending congressional approval of the President’s Fiscal Year 2014 budget. Additional commitments from several foundations and private research institutions have also been secured.

However, the future of this initiative and support for biomedical research in general, including MRI research, is far from guaranteed. Quoting the President of the Society for Neuroscience, Dr. Larry W. Swanson, “scientists will be challenged to make progress on even these initial (BRAIN) projects without sustained and growing financial investment in the scientific enterprise.” One might wonder why investments in the research endeavor should be prioritized when many other economic challenges dominate the world scene. The answer is in the treatments that are desperately needed for diseases like ataxias. Considering one in six people worldwide have a neurological disease, there is also an economic incentive. According to a recent interview with our state senator Amy Klobuchar, “neurological disorders cost the United States about $137 billion a year, not counting the toll on caregivers, and the cost is projected to rise to $1 trillion by 2050.” Considering the rising costs of healthcare

Continued on page 12
in the U.S. and worldwide, novel neuroimaging methods that can help develop drugs to alleviate the burdens of these diseases on society are worth investing.

It is therefore critical to contact our congressmen and women to encourage support for initiatives like the BRAIN initiative and biomedical research in general. According to NIH (www.nih.gov/science/brain/), input will be sought broadly from the scientific community, patient advocates, and the general public during the planning process for the BRAIN initiative – an opportunity for the ataxia community to have our voices heard.

The NIH Blueprint for Neuroscience Research – an initiative that pools resources and expertise from across 15 NIH Institutes and Centers – will be the leading NIH contributor to the BRAIN initiative. I, as an ataxia investigator, have already benefited from this NIH Blueprint initiative, when I responded to a Request for Applications announced under the initiative and applied for funding to study ataxias with MRS. Through this work we identified biomarkers that can be used to non-invasively monitor the brain chemistry and pathology in several hereditary ataxias. We now work on translating the technology for use in clinical trials in ataxias, the next necessary step in bench-to-bedside translation of this novel technology. Therefore while funding for research is tight, initiatives such as these restore our hope in the future and that we will one day conquer these devastating diseases that affect the little brain. In this endeavor, the support of patient advocacy groups such as NAF and individual patients and families, working together with scientists, cannot be underestimated.

What MRI Can Do for Ataxias…
Continued from page 11

MR image from an individual with spinocerebellar ataxia (right) and a healthy individual (left). The atrophy of the cerebellum in the individual with ataxia is apparent from the larger amount of cerebrospinal fluid (bright substance in the image) around the cerebellum.

Free Magazine for Those Affected with Neurological Disorders

Neurology Now is the official publication of the American Academy of Neurology. It is currently available at no cost to individuals with a neurological disorder (including ataxia), their families, and caregivers. To order a subscription, call 1-800-422-2681 or go to www.NeurologyNow.com.

There is also the opportunity to have your personal essay printed in the “Speak Up” section of the magazine. This forum is for people who live with neurologic conditions and those who care for them. Submissions should be kept to 600 words and should be sent to neurologynow@lwwny.com or faxed to (646) 674-6500.

Sharing your story can help raise awareness of ataxia as one of the many neurological diseases that needs more funding for researchers and clinical care information for general neurologists.