ultiple Sclerosis (MS)

ATURE ARTICLE

ay Matter Atrophy May Serve as an Effective Outcome Measure for MS Clinical Trials

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Studies show that gray matter atrophy correlates with disability progression and drives whole brain atrophy in MS.

AMSTERDAM—Gray matter atrophy may serve as an effective outcome measure for clinical trials in multiple sclerosis (MS), said Richard A. Rudick, MD, Vice Chair of the Neurological Institute at the Cleveland Clinic. He described the latest research on gray tter atrophy at the 5th Joint Triennial Congress of the European and Americas Committees for Treatment and Research in ltiple Sclerosis (ECTRIMS/ACTRIMS).

ording to Dr. Rudick, conventional MRI techniques almost entirely overlook gray matter pathology, even though 65% of the in is composed of gray matter. “As a result, all of our focus has been on white matter, and the conventional MRI really just ualizes a small portion of the underlying pathology. [Gray matter pathology] is truly a Trojan horse in MS.”

ough gray matter lesions are still difficult to measure and not discernable using ditional MRI, gray matter atrophy appears to be a highly feasible metric for indirectly ermining the impact of gray matter lesions. “Gray matter atrophy can be measured

cisely with available techniques," said Dr. Rudick.

Rudick described the clinical relevance of gray matter atrophy in MS, including how it relates with lesions, disability, and whole brain atrophy, as well as its potential to igate complications when used as an outcome metric for MS clinical trials.

olving Pseudoatrophy Complications

vious studies have attempted to use whole brain atrophy as a clinical trial measure, but se efforts have been complicated by the issue of pseudoatrophy, which occurs when therapies resolve edema and cause a rapid loss of tissue that resembles atrophy.

vever, a recent posthoc analysis showed that pseudoatrophy was found in white matter her than in gray matter. "So the significance of this, I believe, is that there doesn't pear to be as much fluid shift in the gray matter as in the white matter," Dr. Rudick nmented. "And I think this [difference] would significantly simplify the design of clinical ls focused on atrophy if we were to focus on gray matter."

ed on initial sample calculations, Dr. Rudick expects that future studies will require 60 to 80 patients per arm for moderate ect sizes.

y Matter Atrophy Influences Whole Brain Atrophy

y matter atrophy may serve as a valuable clinical trial metric, because it occurs early in the course of MS and increases as the ease advances, Dr. Rudick explained.

a from an ongoing longitudinal study by Elizabeth Fisher, PhD, of the Cleveland Clinic Lerner Research Institute, and leagues, suggest that accelerating whole brain atrophy over time is mostly driven by gray matter atrophy. The study is mparing healthy controls with patients progressing from clinically isolated syndrome to relapsing-remitting MS, as well as condary and secondary progressive MS.

Rudick noted that white matter atrophy showed little change during the four-year study period. However, "when we look at the y matter atrophy, it explodes, actually. It goes up to fourteenfold, compared with the healthy controls. So the accelerating ophy over time is largely driven by increasing gray matter atrophy."

relation With Disability

y matter atrophy also correlates with MS disability progression, according to six recent cross-sectional studies. In some of the dies, researchers analyzed multiple regression models and found that gray matter fraction, a method of quantifying gray tter atrophy, correlated with clinical outcomes better than other MRI variables, including white matter atrophy.

ddition, seven longitudinal studies have consistently demonstrated that gray matter atrophy shows a stronger correlation with ability progression than does white matter atrophy or lesions. Of the studies, two found that gray matter atrophy predicted nversion from clinically isolated syndrome to MS.

dest Correlation With Lesions

earchers have found that gray matter atrophy correlates somewhat with lesions as well. A three-year longitudinal study by labrese observed 76 patients with relapsing-remitting MS and 31 patients with secondary progressive MS. The investigators ermined that cortical lesions at baseline predicted a change in gray matter volume, though the effect was modest in patients

Quick Poll

Progressive MS

What is the most important outcome measure in progressive multiple sclerosis?

- EDSS
- MRI lesions
- Brain atrophy
- Cognitive performance

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n relapsing-remitting MS and was not significant in patients with secondary progressive MS.

interpretation of this is that there is a connection between cortical lesions and cortical atrophy, but, at least using current hniques, this relationship is rather weak," said Dr. Rudick. He pointed out that current methods for quantifying gray matter ume, such as gray matter fractional volume, may sometimes misclassify lesions due to their signal intensity. The potential for sclassification becomes more problematic in cases of advancing MS with numerous lesions.

elation to quantifying gray matter atrophy, "it's not clear whether gray matter fraction or cortical thickness or region of interest is optimal approach," said Dr. Rudick.

also noted that the effect of drugs on gray matter atrophy might be of interest to researchers. However, not enough data are ilable to draw conclusions.

king forward, he suggested that gray matter atrophy may play an important role in future clinical trials. "I believe gray matter ophy is an attractive outcome measure for MS clinical trials, because it seems to be very important, it's feasible, and I think it uld be fairly straightforward," concluded Dr. Rudick.

—Lauren LeBano

uggested Reading

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