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Commentary

Short Takes

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Dynamic gray mater volume changes in pediatric multiple sclerosis. A 3.5 year MRI study. De Meo E, Meani A, Moiola L. Neurology 2019; 92:e1709-e1723

Flash summary: This study assessed whether childhood multiple sclerosis (MS) affects longitudinal gray matter growth and development. Sixty-eight pediatric patients with relapsing-remitting MS were recruited. Patients underwent magnetic resonance imaging (MRI), and 30 underwent follow-up MRI (median time point 3.5 years). Patients were age and sex matched to 26 controls. In addition, the study coregistered data from normal age- and sex-matched controls derived from NIH databases (the Normal Brain Development Study).

The patients underwent baseline examinations, MRI scans with gray matter volumetrics, and when possible, follow-up examinations and MRI scans. MS lesion assessments were made by a radiologist who was unaware of the patients' other findings. Regional gray matter from healthy controls was used to derive sex-specific normative values.

The pediatric patients with MS showed progressive gray matter atrophy in several brain regions, only partially explained by white matter lesions.

Bottom line: The study was limited because all patients did not undergo repeated evaluations. The study is likely generalizable to childhood MS. It is known that both adult and pediatric patients with MS develop gray matter atrophy. As such this study is confirmatory to many studies performed in adult MS.

The adult MS studies show that subjects with randomly organized gray matter networks show abnormal cognitive function. Therefore MS is a gray matter disease too, and not limited to white matter abnormalities. There is no evidence to date that treatment of MS ameliorates gray matter changes.

As I previously mentioned in this column, my first neurology chairman, “Bud” Rowland, said, “the best way to ruin an academic career was to perform treatment trials in MS.” Heeding his advice, I stayed away from MS treatment research.

We have come a long way with the formation of pediatric MS collaborative research groups. How and when to treat MS lesions is still a matter of debate at least in some subsets of patients. I think the ultimate goal is to stop disease progression, and this is being studied with breakthroughs, even in childhood MS. Up until now the treatment has been primarily geared to improving white matter lesions and motor disability.

With this gray matter data, studies going forward need to incorporate treatment effects on gray matter volume and, more importantly, on cognitive abnormalities. MS plaques alone cannot be the end-point biomarker. MS is much more complex; studies need to look at gray matter changes and the potential for treatment improving MS-related cognitive deterioration.

Rowland was right in the 1980s, but who could have predicted how far our understanding and treatment of MS would come. His sage advice was correct for his times, but the neurological world has made great strides subsequently.

Double-blind randomized, placebo controlled study of trofinetide in pediatric Rett syndrome. Glaze DG, Neul JL, Kaufman WE, et al. Neurology 2019; Epub March 27

Flash summary: This is a multicenter phase 2 trial in girls with Rett syndrome. It is a double-blind, placebo-controlled, and randomized study with 82 patients recruited. Patients were aged five to 15 years. Three doses of the drug were tested; all three doses were compared with the placebo. The results show that the medication was well tolerated at all dose levels. At the highest dose, trofinetide showed statistical, and according to the authors, clinically meaningful improvement, in three Rett syndrome-specific efficacy measures. The parameters measured include Rett Syndrome Questionnaire, Clinical Global Impression of Improvement, and Domain-Specific Concerns Analogue Scale. Some of the measures that showed improvement included repetitive behaviors, breathing problems, mood abnormalities, ambulation, and seizures. The study is deemed a phase 2 trial with placebo arm.

Bottom line: This is a well-done study for a relatively rare disease. It is designed as a phase 2 trial with three doses and assessed tolerability and side effect profiles. The authors included a placebo group, which I always complain about because placebo generally should be reserved for phase 3 trials. However, in rare diseases in children, this approach described here is reasonable and gives

Editor's note: Short Takes offers a brief analysis by Steven G. Pavlakis of selected articles that may be of interest to child neurologists. Articles that strike the fancy of the analyst or the editors are selected for inclusion, but we welcome suggestions.

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information for the next trial design. Of note, the medications seemed to improve symptoms in the highest dose arm. The authors do not claim efficacy, which is reasonable because less than 30 patients were in the high-dose group and outcome measures are somewhat subjective. There is no good outcome biomarker for Rett syndrome. In my experience, seizures, aggression and abnormal behavior, as well as breathing difficulties are somewhat variable and do not worsen in a linear fashion. This makes studies a bit more difficult in a disease that waxes and wanes, where a good outcome biomarker is not available.

Trofinetide is a synthetic analogue of a natural neurotrophic tripeptide. It may work in Rett syndrome because there is a developmental disruption of neurotropic activity, which includes synaptic development and plasticity.

This trial is funded by a pharmaceutical company, and a phase 3 trial is planned at the higher dose. This is a well-designed study for a rare disease where creativity in trial design is required. The combination of a phase 2 with a placebo arm works here. The outcome data are not conclusive because the numbers in the high dose arm are small and because the outcome measures are amorphous (but that is as good as we have).

A couple of points: I find it earth-shattering that, not only was a new clinical entity elucidated during my career, but also that the genetics and pathophysiology are now understood; we even have a potential treatment.

In the early 1990s I saw a boy who died at age one year. He had been diagnosed as having spinal muscular atrophy. I saw the baby and told the parents that he had an unknown brain disease, not spinal muscular atrophy. Several years later, after the boy died, the parents brought his sister to me. She had Rett syndrome, and it was easily diagnosed in the waiting room. So that was my first male (and last) with Rett syndrome. I sent the family for genetic studies, which were being researched at the time. Then Rett syndrome was something not well understood and was only clinically defined. Less than 30 years later, we have a potential treatment trial. In addition, this is a trial that only the pharmaceutical industry would undertake. As such, we need our pharmaceutical industry, especially in these rare diseases. Costs are another issue that we will discuss going forward.