Evidence from an animal model of Rett syndrome suggest that microglia may be involved in the pathophysiology of the disease and that bone marrow transplantation could prove to be a successful treatment in patients.

In experiments with Rett animal models, Jonathan Kipnis, PhD, associate professor of cellular and molecular neuroimmunology, Noel C. Derecki, and colleagues at the University of Virginia, found that symptoms of the disease — stunted growth, tremor, gait disturbances, and breathing problems — were improved following wild-type bone marrow transplantation. The findings were published in the March 18 online edition of Nature.

Rett syndrome, an X-linked disorder caused by defects in the methyl-CpG-binding protein 2 (MECP2) gene, occurs almost exclusively in girls. The disorder is fatal in boys, resulting in microglia and although the neurons are left behind from the normal process of neural cell death or membrane shedding.

The findings suggest that agents that boost phagocytosis might be therapeutic for Rett syndrome. “A lot more work needs to be done,” Dr. Kipnis added. “We are now trying to understand what exactly microglia are doing in the Rett brain. If we prove that debris accumulation due to microglia inability to clear them is indeed one of the underlying mechanisms of Rett, then this may change the field’s perception of the pathophysiology of Rett syndrome.”

**EXPERTS COMMENT**

“Is this a really remarkable result,” said Ben Barnes, MD, PhD, professor of neurobiology and developmental biology at Stanford University. “It is completely unexpected and it suggests that microglia have very important roles in neural function that we do not begin to understand.”

Dr. Mandel added that the new finding shows that neurological diseases are complex from the point of view of cell types and mechanisms involved. “The implications are that therapies are going to have to take this complexity into account and it may be that there will be no one target that can be easily fixed.”

There have been hints from other diseases that glia are involved in the neuropathology and Dr. Mandel’s group decided to revisit the issue in a more directed way, with more experiments and different antibodies. That microglia are involved is interesting, she said, “because they are not derived embryologically from the brain, but from blood.” Plus, she added, “they demonstrated a significant role in recovery of symptoms.”

She said it is too early to know whether replacing the brain with healthy microglia would help children with Rett syndrome. “But there is obviously interest in using bone marrow treatments.”

Alekandra Djukic, MD, PhD, director of the Tri-State Rett Center and associate professor of neurology and pediatrics at the Children’s Hospital at Montefiore Medical Center in New York, agreed. “The results from the bone marrow transplantation are encouraging,” she said. “That they found the immune system has a role in Rett syndrome helps us in understanding the nature of this disease.”

Dr. Djukic noted that she has several Rett patients with severe immunodeficiency and had believed that this was related to their disease. This offers the first proof that she might be right.

Dr. Kipnis and his colleagues treated the animals with bone marrow transplantation before symptoms developed, she said, but they need to repeat the studies in animals that already have signs of the disease to see if it’s possible to reverse the symptoms.

“I do believe that treating Rett is not beyond our reach,” Dr. Djukic said. She has assembled a team of 20 physicians from all fields of medicine to work with the Rett girls and keep their bodies and minds as healthy as possible for when those experimental treatment trials do come along. “Our clinic is preparing to do such a clinical trial in anticipation of the completion of these studies. It feels closer than ever.”

**REFERENCES:**


**DR. ALEKSANDRA DJUKIC** said the investigators treated the animals with bone marrow transplantation before symptoms developed, but they need to repeat the studies in animals that already have signs of the disease to see if it’s possible to reverse the symptoms.