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Imaging Early MS: New MRI Technique Reveals Potential Biomarker of Inflammation and Target for Less Toxic Multiple Sclerosis Treatments

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Imaging Early MS

New MRI Technique Reveals Potential Biomarker of Inflammation and Target for Less Toxic Multiple Sclerosis Treatments

By Brenda Patoine
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An Interview with John Chen, M.D., Ph.D.

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Dana Grantee: 2007-2010

Q: You are studying a brain-imaging technique that has shown promise in animal studies for identifying the earliest signs of brain inflammation from Multiple Sclerosis (MS). How did you get involved in this research?

JOHN CHEN: A significant part of my patient work as a clinical neuroradiologist entails reading brain scans of MS patients. Quite often, we see something on the MRI scan that looks like an active MS lesion–or even several lesions–but the patient doesn't have any symptoms. We also see the converse: the patient's scan shows no active lesions, yet the neurologist reports that the patient is having symptoms. There is a lack of correlation between what we see on conventional MRI and the symptoms a patient presents with.

Q: How would better diagnostic imaging improve treatment of MS?

JC: The clinical experience suggests that the imaging methods we are currently using to identify active inflammation in the brain are imperfect. There are two issues: specificity and sensitivity: how specific are we in detecting active lesions, and are we sensitive enough to detect early signs of disease? Both have implications for MS treatment, because we know that the earlier we treat, the less disability patients will have. If we can reliably, specifically, and sensitively identify active lesions earlier, we can positively influence patient outcomes. That is the goal of this research.

This will also help in clinical trials, by allowing us to more reliably assess how emerging drugs affect the inflammation associated with MS.

Q: Is early diagnosis the biggest challenge right now in MS treatment?

JC: Earlier treatment is associated with better patient outcomes and less disability. Many of the newer therapies for MS alter and curb the normal activity of the immune system. This can have serious, even fatal, side effects. If treatment doesn't start early, the patient may be subjected to serious side effects from the medication without significant benefit.

The biggest challenge in MS treatment today is identifying a good target for drugs that can beneficially treat the disease while

minimizing or avoiding these deleterious immunosuppressive side effects.

Q: Several new drugs for Multiple Sclerosis were approved recently, and still more are in development–many of them potently immunosuppressive. Is MS drug development going down the wrong road?

JC: Right now treatment for MS is at a place where the choice appears to be either take a drug that might make you better but carries the potential of dying from serious side effects, or take drugs that may only improve your functional ability a little bit but has less deadly side effects.

This was especially true with Tysabri (natalizumab), a drug approved by the FDA in 2004. Tysabri stops immune cells from getting to the brain, and was very effective in treating MS.

The problem was that by stopping the trafficking of immune cells to the brain, the immune system's normal surveillance activities in the brain were diminished. As a result, some patients on the drug developed a deadly disease called Progressive Multifocal Leukoencephalopathy (PML), an opportunistic infection most commonly associated with generalized immune deficiency such as AIDS. Tysabri was taken off the market due to this fatal side effect, but because treatment options for MS were so limited, the FDA was pressured to bring it back. It did so in 2006 under a special program designed to minimize risk.[1]

Now we're seeing that many of the new or emerging drugs for MS are based on a similar paradigm of blocking or killing immune cells, especially lymphocytes. These drugs have the potential of really helping patients, but they also have the possibility, in the course of treating a disease that is usually not fatal, of causing serious and possibly fatal infections and diseases.

Q: What does that say about the state of knowledge of what causes MS?

JC: Right now there is still no known cause of MS. The most popular hypothesis is that it is an autoimmune disorder, but environmental toxins, genetics, viruses, or a combination have also been suggested.

What we do know is that, regardless of the cause, the brain becomes inflamed. Inflammation is without question a big part of MS. It is not the cause of MS, but it is a certain sequela of the cause. Inflammation causes the destruction of myelin in the brain and MS results.

Q: The MRI technique you're developing detects an immune system protein called myeloperoxidase (MPO). Why is MPO a target?

JC: Myeloperoxidase is an enzyme that is made by a class of activated inflammatory immune cells called myeloid cells, which include neutrophils, macrophages, monocytes, and microglia. It is expressed at higher-than-normal levels in pretty much any disease that has inflammation as a key component. MPO is implicated, for example, in all phases of atherosclerosis and the progression to heart attack.

Our previous research on MPO in inflammation led us to think that perhaps this enzyme could be important in Multiple Sclerosis. We developed a special imaging technique that can noninvasively detect elevated MPO activity in the brain, and used it to look for the enzyme in the brains of mice with EAE (experimental autoimmune encephalomyelitis), a well-established animal model of MS. The results led us to think that we could monitor and track inflammation during MS attacks.

Q: Under the Dana grant, you investigated how MPO correlates to brain lesions and disease severity in the mouse model. What have you found?

JC: We found that the more MPO there was in the brain, the more severe the disability in the mouse. To us, that meant that MPO levels could reflect disease severity.

That makes this a potential biomarker for disease severity in MS–a goal that has been elusive because the cause of MS is still unknown. The beauty of MPO as a target is that it doesn't rely on knowing what causes MS. Whatever the cause, we know MS is going to lead to inflammation, and inflammation in the brain releases MPO. Using this new imaging tool to monitor MPO levels noninvasively, we hope to be able to assess not just disease severity, but also treatment efficacy.

Q: Looking beyond the potential diagnostic and treatment-tracking applications of MPO imaging, is MPO itself a

drug target?

JC: Our central finding–the more MPO there was in the brain, the more disabled the mouse was–led us to consider that MPO may not just be a bystander, but rather may be involved in the destruction that leads to MS. That suggested the possibility that inhibiting MPO might have clinical benefits in MS, so we started looking at ways to modulate MPO activity in our mouse model of MS and see if we could improve the disease. One compound we tried was a specific inhibitor of MPO that was discovered in the 1970's but never developed into a drug.

To our surprise, the mice all got better–quite a bit better. We didn't cure their disease, but the animals had much lower relapse rates and their symptoms were greatly improved.

Multiple companies are developing MPO inhibitors for various diseases. Earlier this year, investigators reported promising results in animals using an MPO inhibitor to treat Chronic Obstructive Pulmonary Disorder, which also has an inflammatory component. The hope is that accumulating evidence about how MPO works and how inhibiting it can be beneficial in MS could lead to development of MPO-related drugs specifically for MS.

Q: How might this be an improvement over current MS therapies on the market and in the pipeline?

JC: When we block the MPO activity we block the negative consequences of inflammation, but we don't block immune cells from doing their beneficial functions. In fact, humans deficient in MPO live a normal life span. The hope is that targeting MPO would have much fewer side effects and more benign side effects compared to the drug therapies that are currently available.

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[1] In 2010, the FDA issued a "Safety Announcement" alerting the public that the risk of developing PML increases with the number of Tysabri infusions received. This new safety information was based on reports of 31 confirmed cases of PML received by the FDA as of January 21, 2010.

About Brenda Patoine

Brenda Patoine is a freelance science writer who has been covering neuroscience for more than 20 years. She has written for the Dana Foundation since 1989 and is a regular contributor to the foundation's publications and website. She writes both for professional audiences and the general public about advances in brain research, neurology, and the science of spirituality.