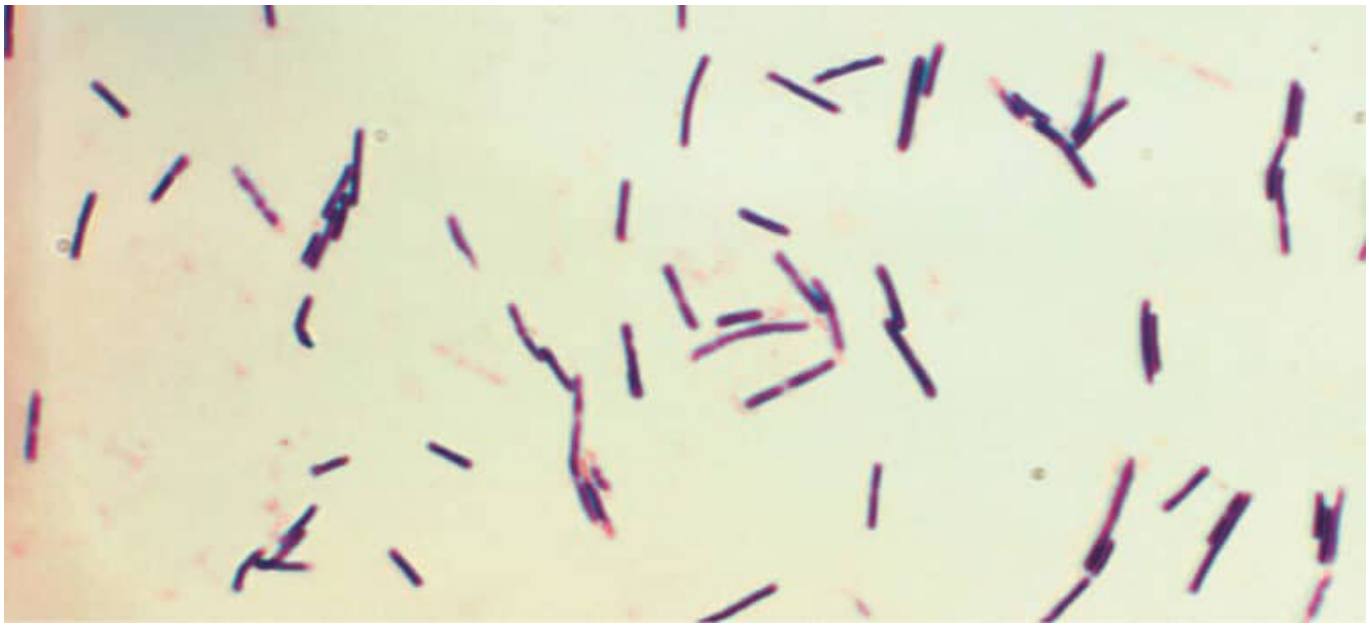
On the trail for the trigger



Researchers look at toxin as possible infectious trigger for MS

by Mary E. King, PhD

One of the hottest areas of research suggests that an infectious agent might trigger multiple sclerosis in susceptible individuals. Could this trigger be a toxin produced by bacteria?

Dr. Timothy Vartanian, professor of neurology and neuroscience, and director of the Judith Jaffe Multiple Sclerosis Center at Weill Cornell Medical College and New York Presbyterian Hospital, and his colleagues—Kareem Rumah, MD, a PhD candidate at Weill Cornell Medical College and Rockefeller University; and Vincent Fischetti, PhD, professor and chairman of the Laboratory of Bacterial Pathogenesis and Immunology at Rockefeller University—think it is indeed possible, and are intent on finding out.

Why look for an infectious trigger?

The search for an infectious trigger is not new in MS research. Much inquiry has focused on the possibility that unknown infectious agents such as viruses or bacteria might trigger the disease, though MS is not believed to be contagious. Recently, MS researchers from Australia found intriguing evidence for a possible trigger when they were able to study very new lesions, or spots of disease activity, from the brains of people with MS who had an acute exacerbation but then died (from any cause, MS-related or not) within 24 hours of the flare-up.

Dr. Vartanian explains that when scientists examined those newly forming MS lesions, they

found two important changes that are typical of most MS lesions: disruption of the blood-brain barrier and oligodendrocyte death. (The blood-brain barrier is a tightly packed layer of cells that prevents certain substances in the blood from reaching the brain. Oligodendrocytes are the cells that make myelin, the substance that surrounds nerve fibers. Myelin is a major target of the immune attack in MS.) However, the Australian researchers did not find macrophages or lymphocytes, two types of cells found in older MS lesions that are typically related to autoimmune responses.

“These clues lead us to think that the first event in the formation of a new lesion is triggered by an environmental factor, rather than an autoimmune response, after which the classic autoimmune response develops,” suggests Dr. Vartanian.

Historical foundations

Evidence supporting an infectious trigger comes from many sources, including studies of MS epidemics on the Faroe Islands. No MS cases were documented there prior to 1943, despite the fact that the neighboring countries of Iceland, Sweden and Denmark had a high incidence of MS at that time. All of these populations had a common Norse ancestry. After British troops arrived on the islands during World War II, four sequential MS epidemics were documented. Given the population’s genetic stability during this period, the sudden appearance of MS on the islands strongly suggests that an infectious (or other environmental) trigger was necessary for MS to occur, explains Dr. Vartanian.

A likely candidate

But what could that trigger be? Many different viruses and bacteria have been proposed, and it’s even possible, Drs. Vartanian and Rumah note, that a molecule called epsilon toxin is a good candidate. The toxin is produced by two specific subtypes of **Clostridium perfringens**, a common bacterium.

The epsilon toxin is uniquely qualified to be a potential trigger for MS, he explains. It can breach the blood-brain barrier, enter the brain and kill oligodendrocytes. Also, it only attacks the central nervous system, not peripheral nerves (such as those in the arms and legs). This means that both epsilon toxin’s mechanism of action and the location where it acts match what is already known about MS lesions.

Dr. Vartanian’s research team, which includes Dr. Rumah, as well as Jennifer Linden, PhD, Yinghua Ma, PhD, and Myat Lin Oo, PhD, is conducting experiments to test the epsilon toxin hypothesis. Rumah and Linden were the first to find intriguing evidence of this toxin-producing organism in a woman newly diagnosed with MS. Rumah determined that about 10 percent of people with MS show signs of exposure to the toxin compared with only 1 percent of healthy individuals. Dr. Vartanian states that these numbers are likely underestimates of true exposure because the markers for exposure disappear fairly quickly in the blood.

Drs. Linden and Ma showed that exposing healthy mouse brain to the C. perfringens B strain, one of the subtypes that produces epsilon toxin, led to the death of oligodendrocytes and to loss of myelin, mimicking the changes seen in MS. The researchers were able to block these detrimental effects by treating mice with antibodies that neutralize the toxin.

Origins of epsilon

From other research, scientists know that C. perfringens is a very common bacterium that is found in soil, marine sediment and the gastrointestinal tracts of ruminant animals such as sheep, goats and cattle.

C. perfringens can make its way into food products if the food is contaminated by the contents of an infected animal's GI tract. The two subtypes of C. perfringens that make the epsilon toxin, called B and D, are closely related to a different subtype, called C. perfringens A, which causes a foodborne diarrheal illness but does not make epsilon toxin.

Zuha Anwar, a high school student working in Dr. Vartanian's lab under Dr. Linden's guidance, found evidence of C. perfringens type D in some food samples. "The data are very preliminary," says Dr. Vartanian, "and much more work needs to be done to determine whether epsilon toxin is a trigger for MS, and precisely how humans become exposed. In addition, there is no current evidence for any connection between food contamination and MS."

Next steps

Dr. Vartanian and his team are in the early stages of developing a sensitive blood test for exposure to epsilon toxin, something that is very difficult to measure currently. They are also creating a mouse model that may enable them to further study how MS lesions form and develop over time.

Dr. Vartanian elaborates, "We hope that in two or three years, we and others will be able to determine whether epsilon toxin is truly associated with MS, which would give us a critical new pathway to developing strategies to [block this toxin]." This capability in turn could prevent lesion formation and, ideally, development of MS in susceptible individuals.

Mary E. King, PhD, is a freelance medical writer in Boulder, Colorado.