Scientists develop animal model for TB-related blindness

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(Medical Xpress) -- Working with guinea pigs, tuberculosis experts at Johns Hopkins and elsewhere have closely mimicked how active but untreated cases of the underlying lung infection lead to permanent eye damage and blindness in people.

Lead study investigator and Johns Hopkins infectious disease specialist Petros Karakousis, M.D., says the new animal model should hasten development of a badly needed, early diagnostic test for the condition. Symptoms of ocular TB — vision loss, and redness and pain in the eye — are often indistinguishable from symptoms of other chronic infections and inflammatory conditions, including toxoplasmosis and sarcoidosis, which can often lead to selecting the wrong therapy.

“TB infection can be active in the eyes even in the absence of lung symptoms,” says Karakousis, an assistant professor at the Johns Hopkins University School of Medicine. “So, there are usually long delays in diagnosis, and by this time, it’s too late for tens of thousands of people who are already going blind due to permanent inflammatory damage to the inner lining of the eyes.”

The scenario, he noted, is especially true in the United States and Europe, where TB is far less common than in developing countries, where most of the 9 million new infections occur each year. Most new cases in the United States occur in people whose immune systems are already depressed from co-infection with HIV and who lack access to antibiotic treatments. Some 20 percent of people with the potentially

deadly lung infection, caused by Mycobacterium tuberculosis, develop inflammation in other organs, including in the inner tissue linings of the eye or linings surrounding the brain.

The Johns Hopkins team's description of the animal model for ocular TB appeared in the Public Library of Science One online last week.

Karakousis says a clear and rapid test for ocular TB would not only prevent treatment delays, but also reduce the rate of misdiagnosis. Suspected inflammatory disease, such as sarcoidosis and lupus in the eye, are treated with steroids, which can promote bacterial spread across other body organs, making the infection worse.

Current diagnostic methods for ocular TB involve a lot of guesswork, says Karakousis. Underlying signs of active TB in the lungs, such as positive chest X-rays and sputum samples, are helpful in making a diagnosis but often not present. Tissue biopsy of the affected part of the eye offers more reliable confirmation of infection, but the procedure involves painful needle extraction that carries the risk of permanent eye damage, even blindness. Physicians are often deciding to treat based on a high suspicion of TB infection, and then taking a "wait and see" approach for several weeks or months to determine if people are getting well or not.

Karakousis and his team used small, aerosolized doses of about 200 bacteria to infect each animal's lungs, a procedure closely replicating human TB infection, which is spread when uninfected people inhale small numbers of the organisms coughed up by people already infected. Karakousis says all previous animal models for studying TB infection, in mice and in rabbits, used more than 10 times larger doses of injected tubercle organisms to eventually infect the eyes, which is not really how the disease spreads to the eyes.

Microscopic testing of eye tissue samples showed all guinea pigs were infected with TB after two months, and that the disease spread through the bloodstream, as it does in humans.

Moreover, small, grainy nodules, a telltale sign of active TB infection, were observed in both the lungs and in the inner choroid tissue layer lining the eyes. Some choroidal tissue death and thickening, as well as bleeding from blood vessels, were also seen — all known indicators of active TB infection in humans.

Further tissue analysis of lung and eye granulomas revealed increased production of vascular endothelial growth factor, or VEGF, a signaling protein linked to irregular blood vessel formation and known to play a role in other vascular-related vision problems, such as blindness due to diabetes and age-related macular degeneration.

Karakousis says ophthalmologists have already had some success with VEGF antibody treatments, used in combination with standard antibiotics, to treat TB infection in the eyes and the lungs. He adds that anti-VEGF drugs could represent new therapies for ocular-TB-related disease and that VEGF levels in the eye could signal active TB infection in the eye. The Johns Hopkins team next plans to test VEGF and other protein levels in eye fluid as possible diagnostic test markers for ocular TB.

“Having a verifiable diagnostic test for ocular TB is key to picking up on active infections early and providing treatment that stands the best chance of preventing long-term damage, with our without any signs or symptoms of lung infection,” says Karakousis. “Until then, physicians will have to be aware to test for ocular TB, especially in regions like Africa and Southeast Asia where the disease remains endemic, and to listen for clues in the patient’s life history that might alert them to earlier possible TB exposure.”

TB is the leading cause of death among people co-infected with HIV, the virus that causes AIDS, and is responsible for an estimated 2 million deaths annually, including a half-million in those infected with both organisms.

Provided by Johns Hopkins University

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