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Researchers explore link between schizophrenia, cat parasite

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Johns Hopkins University scientists trying to determine why people develop serious mental illness are focusing on an unlikely factor: a common parasite spread by cats.

The researchers say the microbes, called Toxoplasma gondii, invade the human brain and appear to upset its chemistry -- creating, in some people, the psychotic behaviors recognized as schizophrenia.

If tackling the parasite can help solve the mystery of schizophrenia, "it's a pretty good opportunity ... to relieve a pretty large burden of disease," said Dr. Robert H. Yolken, director of developmental neurobiology at the Johns Hopkins Children's Center.

The cause of schizophrenia is unknown, but both genetic and environmental factors likely play a part, according to the National Institute of Mental Health. Yolken is among the researchers worldwide examining whether certain viral infections can increase the risk of developing the illness. Other studies have focused on flu and herpes viruses as possible triggers.

The notion that there are links between infections and schizophrenia is "intriguing," said Dr. Ken Duckworth, a clinical psychiatrist and medical director for the National Alliance on Mental Illness. "There's so much we don't know about schizophrenia that anybody paying attention would welcome any thoughtful inquiry. And the infectious disease corner of the field is a growth stock right now," he said. "If true, it would have a

preventive implication which is profound."

In a study of 12- to 49-year-olds who were born in the U.S., about 9 percent were found to be infected with T. gondii in the early 2000s, according to the Centers for Disease Control and Prevention. That rate is down from 14 percent in the 1990s. However, Yolken believes infection rates are higher among older Americans.

Yolken, a cat owner who says he has tested positive for Toxoplasma antibodies, said the potential link between Toxoplasma infections and mental illness is no reason for cat owners to panic -- they just need to keep some basic hygienic precautions in mind.

He was drawn into the field by some intriguing questions about schizophrenia.

"I couldn't understand why a disease like schizophrenia persists in humans," he said. Through much of our history, "people who have these diseases don't reproduce very well, either because they're sick, or they've been locked up, or because they were killed."

If the disorder were strictly genetic in origin, he added, those genes should have been culled from the gene pool long ago. But they weren't. That raises the question of an environmental, perhaps infectious origin -- a germ that has evolved to benefit by infecting other species.

It was a colleague, Dr. E. Fuller Torrey of the Stanley Medical Research Institute in Chevy Chase, who sealed the deal for Yolken by unearthing a trove of studies from as far back as the 1950s, many of them not written in English, suggesting links between infections and schizophrenia.

Schizophrenia, a severely disabling brain disorder characterized by confusion, delusions and hallucinations, afflicts 1.1 percent of the U.S.

population age 18 and older, according to the National Institute of Mental Health. Someone with a toxoplasma infection, called toxoplasmosis, is more than twice as likely to develop schizophrenia, according to Yolken.

First isolated in 1908, T. gondii is present in the bodies of a third of the world's population, on average. It is a lifelong infection.

"Humans can get infected either directly (from contact with cat feces), or from eating the (undercooked) meat of an animal that was itself infected by a cat," Yolken said. Some toxoplasmosis outbreaks have been traced to water supplies contaminated by cat feces.

When they're initially infected, most people have little more than flulike symptoms, or none at all. But young children, people with weakened immune systems and women infected while pregnant can develop a brain inflammation called encephalitis, or suffer miscarriages, damage to the heart, liver, eyes or ears. Infection can be fatal, and fetuses that survive their mother's first infection may be born with retardation, deafness and other problems.

Felines are typically infected when they eat an infected mouse or bird. They don't usually get sick. So far, there is no vaccine to prevent cats from becoming infected. So the microbe reproduces in the cat's gut. Its eggs, or oocysts, develop there, and are later shed with the cat's feces.

When another warm-blooded animal such as a mouse ingests the oocysts through contact with cat feces, the oocysts enter its gut. There they release cells that migrate mostly to muscles and the brain, forming cysts to protect themselves from the mouse's immune system.

But T. gondii must get back into a cat to reproduce again. To get there, it needs the mouse to be eaten by a cat. Scientists believe the parasite

raises its odds of success by changing the mouse's behavior and reversing its natural fear of cats.

But how?

Studies of mice and rats infected by T. gondii have shown risky behavior changes, including an attraction to the smell of cat urine that makes them vulnerable to attacks. These findings may have parallels in behavioral changes in people, from schizophrenia to depression and reflex impairment.

Glenn McConkey, a researcher at the University of Leeds in England, reported last year that two genes in T. gondii's DNA contain instructions for the production of an enzyme that makes a brain chemical called dopamine.

"That's somewhat unusual, because other parasites don't have that (dopamine)," said Sarven Sabunciyan, Yolken's colleague at Hopkins. After all, microbes have no brains.

But in higher animals with nervous systems, dopamine is a neurotransmitter with important roles in regulating behavior. Some anti-psychotic drugs used to treat schizophrenia work by blocking dopamine action in the brain.

Medical students have long been told that mental illness and infectious disease were separate fields.

"I was taught they had nothing to do with each other," said Duckworth, at NAMI. But then he'd encounter a Lyme disease patient with something resembling psychosis, or an AIDS patient with depressive symptoms. "I think it's intuitively possible. After my experience with AIDS patients, I can think, 'Why not?' "

Recent studies have found that a variety of viral infections, early in life, appear to carry risks of brain changes.

In May, Hopkins researcher David J. Schretien published a study suggesting that some brain changes and cognitive symptoms in schizophrenics may be caused or worsened by exposure to a herpes simplex virus. A 2005 Czech study found evidence of personality changes in humans infected by another herpes virus called cytomegalovirus. And numerous studies have suggested that flu infections during pregnancy may increase a child's risk of schizophrenia and autism.

Evidence that T. gondii infections may be a cause of schizophrenia, while not yet conclusive, is growing, Yolken said. A review of past studies, published last year by Yolken and Torrey, collected a variety of intriguing correlations. For example: People with schizophrenia have a higher prevalence of T. gondii antibodies in their blood. There are unusually low rates of schizophrenia and toxoplasmosis in countries where cats are rare, and unusually high rates in places where eating uncooked meat is customary. And some adults with toxoplasmosis show psychotic symptoms similar to schizophrenia.

Studies have linked a history of toxoplasmosis with increased rates of other mental changes, too, including bipolar disorders and depression. A 2002 study in the Czech Republic noted slowed reflexes in Toxoplasma-positive people and found links between the infection and increased rates of auto accidents.

A University of Maryland study last year found that people with mood disorders who attempt suicide had higher levels of T. gondii antibodies than those who don't try to take their own lives. Still, the links between schizophrenia and toxoplasmosis are not simple. For example, most people infected with T. gondii never become schizophrenic. And not all

schizophrenics have been exposed to toxoplasma.

Yolken believes additional factors, such as an unlucky combination of genes, are probably needed to produce schizophrenia among Toxoplasma-infected people. The parasite's DNA may also be important, since some strains are known to cause more disease.

Studies have also suggested that the timing of the infection -- early in life when the brain is developing -- and the place in the brain where the cysts settle, may be important, he said.

But once the T. gondii cysts are established, how might medical science find and kill, or at least silence them?

Yolken said that while T. gondii cysts are invisible to the immune system, they are not totally passive. Inside the cysts, the microbes are alive, sensing their environment, periodically trying to break out, multiply and form more dopamine-making cysts. The flare-ups probably occur when the host's immune system is weakened by illness or stress.

Scientists believe these "reactivations" of the infection could explain the emergence or worsening of cognitive symptoms as people with schizophrenia reach adolescence and young adulthood.

Researchers have also noted that toxoplasmosis is similar to malaria in its persistence in the body, its flare-ups, and its ability to hide from the immune system, Yolken said. So Sabunciyan and researchers elsewhere are investigating whether anti-malarial drugs might work against T. gondii cysts.

Sabunciyan has reported promising results with a class of anti-malarial drugs, called artemisinins, which appear to be effective at killing T. gondii in tissue cultures. "The next step is to do that in animals," Yolken

said.

If it works in animals, that would raise hopes for a toxoplasmosis treatment for people, and perhaps, one day, some relief for people with schizophrenia.