Depression: Allergic Reaction? Infectious Disease?

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Researchers are exploring exciting lines of evidence suggesting that depression is not simply an imbalance of neurochemicals in the brain but possibly fallout from an inflammatory response mounted by the body to deal with stress.

Investigators at the Icahn School of Medicine at Mount Sinai, in New York City, recently linked differences in the peripheral immune system in a mouse model to susceptibility to social stress, findings they correlated with serum cytokine levels in patients with treatment-resistant depression.

Other experts go a step further and promote the idea that the inflammatory state underlying depression may be caused by a pathogen such as a parasite, bacterium, or virus.

This evolving research thrust could have huge implications for depression treatment. It could change an almost totally symptom-based paradigm into one based more on biology.

Biology-Based Diagnosis

"It means that clinicians should start diagnosing based on biology and not on behavioral symptoms," said Scott Russo, PhD, associate professor of neuroscience, Icahn School of Medicine at Mount Sinai, told *Medscape Medical News*.

Dr Russo led the research team that carried out the mouse experiments, the results of which were published online October 20 in the *Proceedings of the National Academy of Sciences.*

After drawing blood from experimental mice and checking for levels of interleukin 6 (IL-6), researchers put the rodents separately into the cage of a larger, more aggressive mouse, allowing physical contact for 10 minutes a day for 10 days.

Some mice showed symptoms similar to those found in depressed patients, such as social avoidance.

"The mice also no longer preferred sugar water and didn't want to have sex, and it took more to stimulate them in terms of the pleasure centers in the brain," first author of the article, Georgia Hodes, PhD, postdoctoral researcher in neuroscience, Icahn School of Medicine, told *Medscape Medical News.*

"These animals were in a state that seems to be somewhat similar to depression."

What separated these mice from those that did not develop these symptoms were differences in the peripheral immune system. Even before they were put into the stressful situation, these susceptible mice had more white blood cells than those that were resilient.

"When we stimulated those white blood cells, they released more IL-6, and it predicted which animals would go on to become susceptible and which would go on to become resilient," said Dr Hodes.

The researchers then checked serum IL-6 levels of patients with treatment-resistant major depressive disorder (MDD) and found higher levels than in healthy control individuals.

Allergic to Stress

"The analogy I make is that it's an allergy to stress, that the body somehow perceives stress as being more dangerous than it is, and it mounts a much larger immune response to try to protect you from this stress, but as a result, you're getting these symptoms that we associate with depression," said Dr Hodes.

The animal research suggests that the inflammation precedes the response to stress, so it is not a result of it. This seems to be the case in humans, too. Dr Hodes cited a recent longitudinal study published in *JAMA Psychiatry* (2014 Oct;71:1121-8) that measured IL-6 levels of 9-year-old children and looked at these levels again when they were 18 years old.

"The kids who were in the group with the highest circulating levels also had the highest levels of psychosis and depression" in early adulthood, she said.

Dr Hodes' team also showed that emotional response to stress can be blocked. They treated the mice with an antibody that neutralizes IL-6 in the periphery and stops it from getting into the brain. "By doing that, we could make our animals resilient," she said.

Monoclonal antibody drugs that target IL-6 in humans are being used to treat rheumatoid arthritis (tocilizumab [*Actemra*, Genentech, Inc]) and Castleman disease (siltuximab [*Sylvant*, Janssen Pharmaceuticals, Inc]), a condition caused by hyperactivation of the immune system. This, said Dr Russo, raises the possibility that these agents may be useful for patients with depression.

"We would be excited to do some off-label studies to see if they actually are effective in reversing depression in this subcategory of treatment-resistant patients who have a heightened inflammatory load."

Although IL-6 might be a key player, Dr Hodes is convinced that it is not the only cytokine involved in this immune response. Tumor necrosis factor–alpha (TNF-α), for example, may also play a role. In fact, a double-blind, controlled trial of patients with psoriasis found improved symptoms of depression and fatigue in those taking etanercept (*Enbrel*, Immunex Corp), a TNF-α inhibitor (*Lancet* 2006 Jan 7;367:29-35).

Patients with rheumatoid arthritis or psoriasis, as well as those with asthma, often also suffer depression, noted Dr Hodes. "But it has been hard to determine whether the depression they experience comes from the inflammation or is a result of the symptoms they have," she said.

The new research may help explain why current depression treatments that operate on the premise that dopamine or serotonin levels need normalizing do not work for all patients. It could be because these agents are not targeting the cytokines that are causing the neurochemical imbalances, said Dr Russo.

"It might be that these immune responses, or this allergy to stress, are what needs to be corrected, and then you have more healthy positive downstream effect on brain tissues."

Heterogeneous Disease

The new information may help push the field of psychiatry away from an emphasis on symptoms such as sadness, added Dr Russo.

"If we started to move more into diagnosing based upon biology, we would see that people who are depressed are actually reflective of a heterogeneous disease caused probably by hundreds, if not

thousands, of things, IL-6 being one of them. And if we started to identify that and had diagnostic predictors of disease, we might be better able to treat it in the future," he said.

Although blood tests are now being used to rule out thyroid levels underlying psychiatric illnesses, this does not go far enough, said Dr Russo.

"What we're saying is that rather than using biology as a rule-out for depression, we should use it as diagnostic criteria that prove a person is actually depressed, rather than just asking them if they're sad."

It's not yet clear which factors influence heightened cytokine levels in the first place, though. According to Dr Russo, maternal milk quality, early life experiences, and even whether the father was stressed have all been investigated as possibly playing a role. "These are factors that we're thinking about, although we haven't validated them."

But they're factors that Dr Hodes hopes to address in her laboratory. She also wants to look at sex differences.

"There's a high incidence of autoimmune disease in women and a high occurrence of depression. I'm interested in looking at how sex differences in the immune system may be contributing to that," she said.

Pathogen Activator

Another factor that should be pursued is a pathogen, according to Turhan Canli, PhD, associate professor of psychology and radiology, Stony Brook University, New York.

In a recent article in *Biology of Mood and Anxiety Disorders*, Dr Canli outlined how inflammatory markers such as IL-6 and TNF may represent activation of the immune system in response to a parasite, bacterium, or virus.

Dr Canli provided examples of how pathogens might affect their host's behavior, brain systems, and neurotransmitters. One example is the parasite *Toxoplasma gondii*, which researchers have linked to schizophrenia.

"It would be remarkable if it ended up being just one thing," Dr Canli told *Medscape Medical News.*

"Any number of constellations of symptoms would constitute the diagnosis of major depressive disorder, so I think, realistically, it's probably going to be an entire class of pathogens, each of which has some capability of affecting brain processes or brain structures in one way or another," he said.

Dr Canli was struck by the lack of progress in developing effective treatments for depression. Research shows that antidepressant drugs do not work any better than placebo for mild to moderate depression, and this has been the case for decades, he said.

Also, even when people do feel better after taking an antidepressant, there is a good chance the relief will not last long.

"There’s a 50% recurrence rate over a lifetime; that doesn't suggest that you're curing anything," said Dr Canli.

This, he stressed, strongly suggests that researchers simply do not know the underlying mechanisms leading to depression. In his mind, the pathogen mechanism is as plausible as any.

He is not alone. Since the publication of his article promoting this theory, he has received "a ton" of responses, most from patients but some from clinicians, assuring him that he is "onto something," he said.

He is now in the process of developing a research agenda for a study that, if funded, will investigate the role of a virus (he's tight-lipped about exactly which one) in depression.

Need for a New Paradigm

Asked for his thoughts on this evolving research topic, Peter Kramer, MD, clinical professor of psychiatry and human behavior, Brown University, Providence, Rhode Island, author of *Listening to Prozac* and *Against Depression*, and a member of the American Psychiatric Association, said the concepts it espouses are not new.

"It's not as if, all of a sudden, the field has been blindsided by some theory that emerged yesterday."

According to Dr Kramer, the theory connecting infection and psychiatric illness dates back at least to the 1990s. One of the first examples was when patients with hepatitis and melanoma treated with the older interferon, which is a cytokine, felt sick and depressed, and when they stopped the drug, these symptoms resolved.

This gave rise to the "malaise theory of depression", said Dr Kramer.

The relationship between inflammation and depression could be due to a link between the neurologic and immune systems, he said.

"It could be that people who are vulnerable to stress show it in their neurological responses and in their immune responses and those are paired in some way. We used to talk about the immune system being the distant reaches of the neurological system, that the brain would reach out through nerves and the immune system. It could be that one alerts the other."

Also weighing in on the debate for *Medscape Medical News* was Paul Garfinkel, MD, professor of psychiatry, University of Toronto, in Canada, and staff psychiatrist, Centre for Addiction and Mental Health, who said he is excited about these emerging theories. Psychiatry, he said, is in need of a new paradigm.

The old model, or the monoamine hypothesis, according to which depression is caused by depletion of neurochemicals such as serotonin, "is a bit tired and in need of a refresh," said Dr Garfinkel. "It has provided some value, but a lot of the corroborating support hasn't been there, and the new drugs haven't been so useful."

Three lines of evidence point in favor of an inflammatory connection, said Dr Garfinkel. The line of evidence that people with depression have higher inflammatory markers was reinforced in a Danish study of more than 70,000 people, he said.

That study found that those with a high level of C-reactive protein, a marker of inflammation, were up to three times more likely to have depression (*JAMA Psychiatry.* 2013;70:176-184).

Other lines of evidence include a link between inflammatory diseases such as rheumatoid arthritis and heart disease and depression and the fact that anti-inflammatory medications have been shown to improve depressive symptoms.

But although inflammation is an "intriguing model," another emerging paradigm — neurogenesis — is also promising, said Dr Garfinkel. According to this model, growth of immature cells in the hippocampus can be stimulated to ease depressive symptoms.

"To have these 2 models — neurogenesis and inflammation — which can lead to new treatments is very exciting."

Dr Canli's TED talk on depression as an infectious disease can be viewed here: http://youtu.be/1dD29XHp6CU.

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