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Antibiotics or Infection Itself? The Possible Importance of Inflammatory Cytokines on Mental States

To the Editor: We read the recent report by Lurie and coauthors¹ with great interest. We completely agree with the authors that recurrent antibiotic exposure can increase the risk of depression and anxiety via changes in intestinal microbiota. The authors obtained their results based on very large cohort studies carried out over many years.

However, we are afraid that they overlooked the importance of infections that require up to 5 courses of antibiotic administration. Though acute or chronic infections often affect the mental status of the host by inducing proinflammatory cytokines, change in the intestinal microbiota caused by antibiotic treatment is often reversed after short administration-free periods.²

Thus, we cannot exclude the possibility that depression and/or anxiety are associated with the severe infectious diseases and are mediated via the induction of various cytokines. Unfortunately, Lurie and colleagues' report completely lacks the clinical diagnosis and/or pathogens that were targeted by the antibiotics.

Increased levels of proinflammatory cytokines and chemokines, as well as acute phase proteins and cellular adhesion molecules, have been reported in patients with depression.³ Local cytokine concentrations in the central nervous system (CNS) do not correlate with peripheral blood levels. However, under some conditions, cytokines can cross the blood-brain barrier, enter the CNS, and affect neural functions by altering neurotransmitter metabolism, neuroendocrine function, and synaptic plasticity. In addition, during CNS inflammation, such as encephalitis and meningitis, cytokines and chemokines produced in situ might cause permanent brain damage.

Another interpretation is that the serious bacterial infection, which required antibiotic treatment, might have caused the depression and anxiety. For example, Goodwin⁴ suggested an association between an increased risk of depression and anxiety during childhood and adolescence with previous severe infection events. In adults, an increased risk of depression and anxiety has also been associated with chronic infectious disorders, including tuberculosis.^{5,6} Further, patients admitted with major psychiatric

disorders, including schizophrenia, bipolar disorder, depression, or anxiety, have been reported to have an increased risk for pneumococcal infections, even if they are under 60 years of age.⁷

Taken together, while we must avoid needless administration of antibiotics, we need not hesitate to use them in patients with bacterial infections, because infections can increase the risk of mental disorders by inducing proinflammatory responses at the systemic or CNS levels.

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