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Gastrointestinal Disorders and “Medical Depression”

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Moving beyond recent formidable work in animal models, Lurie and colleagues¹ provide evidence from a sizable human database that recurrent antibiotic exposure is associated with increased risk for depression and anxiety. This focus on the “gut-brain axis” is exciting and deserves to be viewed in the context of earlier explorations of the links between gastrointestinal disease and psychiatric conditions.

Perhaps the most pertinent and intriguing body of past work is that dealing with the puzzling, still unresolved relationship between pancreatic cancer and depression.^{2,3} Long before the advent of psychotropic medications, Yaskin⁴ in 1931 reported that clinical depression may be the earliest manifestation of a pancreatic carcinoma. Later work demonstrated that pancreatic cancer is the entity with the highest incidence of depression among all tumors of the digestive system.⁵ Louhivuori and Hakama⁶ reported that gastrointestinal malignancies confer the greatest risk of suicide among all cancers.

Pancreatic carcinoma is a challenging condition to diagnose, often requiring more than 18 months to establish the diagnosis. In retrospect, clinicians have often thought that depression was its heralding sign. This temporal sequencing has been used to argue against depression as a “reactive response” to the psychological insult of the cancer. (The patient is not aware of the diagnosis for months.) The basis for the association between depression and pancreatic carcinoma has been presumed to involve a paraneoplastic process with gut neuropeptides, which are comparable, if not identical, to brain neuropeptides.

The work of Lurie et al¹ introduces anew the question of the role of gut neuropeptides in depression. In turn, the link between depression and pancreatic carcinoma leads to the broader question of “medical depression.” Is depression arising in the context of a medical illness a discrete or different clinical entity versus depression that emerges in the patient free of any medical condition? Medical depression is curious in that it has no gender preponderance and few genetic linkages, but it has specific electroencephalographic accompaniments and appears to respond less favorably to

psychotropic interventions than depression in those without concurrent medical illness.⁷

Over the past 10–15 years, depression in the medically ill has come to be seen as a two-way street or a bidirectional process. Those with primary medical conditions are at increased risk for the development of clinical depression (not merely as a reactive response but because of intrinsic physiologic changes—including, perhaps, those in gut flora?), and those with depression are at increased risk for an acceleration of their medical illness or other adverse sequelae. Much attention has been directed to the interplay between depression and coronary artery disease.^{8–10}

Rates of depression in the setting of different medical illnesses vary widely.¹¹ Highest rates are encountered in Cushing’s disease (approaching 70% prevalence), but in other conditions rates of depression barely exceed those found in the general population.¹¹ Rates of depression in neurologic illnesses are surprisingly consistent, ranging from 30%–50% prevalence in Huntington’s disease, Parkinson’s disease, stroke, dementia of the Alzheimer type, and multiple sclerosis with cortical involvement.¹¹ These conditions, of course, have in common structural changes or lesions of the central nervous system, not merely changes in neurotransmitters.

With regard to other forms of bowel disease, there is an older literature linking inflammatory bowel disease and irritable bowel syndrome with psychiatric disorders and symptomatology.^{12–14} More recent work in this domain again underscores the theme of bidirectionality of psychiatric and, in this case, gastrointestinal comorbidities.¹⁵ Alterations in gut flora (dysbiosis) induced by the administration of antibiotic therapy may prove to be a fascinating window into the larger question of the physiological alterations driving the emergence of clinical depression. We now know that clinical depression evokes or brings extensive changes to immune, autonomic, and hematologic functions—conversely, altering the basic physiologic integrity of organ systems seems quite capable of inducing psychiatric disorders.

Lurie and colleagues¹ close by calling for studies of microbiota composition in psychiatric disorders. In addition, the issue of treatment interventions must be addressed. Will the changes in gut flora resolve of their accord or will corrective measures be required?

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