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Dose Irritable Bowel Syndrome and Dysmotility Have an Autoimmune Origin?

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Summary

The etiology of irritable bowel syndrome (IBS) and dysmotility has not been well-established. Organic, pathognomic changes have not been described. Recently, Ohlsson et al[1] suggested that higher levels of gonadotropin-releasing hormone (GnRH) IgM antibodies in serum were detected in patients with IBS and dysmotility, but not in organic gastrointestinal (GI) diseases, compared with healthy controls. They evaluated the presence of IgM and IgG antibodies against GnRH in serum using an ELISA method from healthy subjects and patients with GI diseases. The prevalence of GnRH IgM antibodies were higher in IBS and dysmotility patients than those in healthy controls (42% vs 23%, $P = 0.008$), and the expressed levels were higher ($P = 0.000$). Patients with celiac disease or inflammatory bowel disease had the same or lower levels of antibodies.

The authors concluded that antibodies against GnRH were common in patients with IBS and dysmotility, but not in organic diseases, compared with healthy controls, which might explain the symptoms in a subgroup of patients with these diseases. These findings suggested that IBS and dysmotility to some extent might be of an autoimmune origin.

Comment

IBS is a chronic functional GI disorder characterized by episodic abdominal pain or discomfort in association with altered bowel habits. The pathophysiology is poorly understood, there are no disease-specific biomarkers, and diagnosis depends solely on symptom-based criteria. A variety of factors are believed to play a role in the development of the IBS symptoms including altered bowel motility, visceral hypersensitivity, psychosocial stressors, altered brain-gut interactions, low grade inflammation, alteration in the gut microbiome and genetic factors.[2] Gastrointestinal motility requires coordination between the intrinsic and the extrinsic nervous system, the interstitial cells of Cajal and smooth muscle cells.[3] The etiology of dysmotility has been suggested as autoimmunity or inflammation, although it is unknown in most cases.[4] The concept that inflammation plays a role in IBS has raised interest in the immune system as a source of biological markers for this condition.[5] Recently, high-sensitivity C-reactive protein levels of serum had been higher in IBS patients than healthy controls. This might reflect that the low-gut inflammation is believed to occur in IBS and support its existence. But the blood levels were still in the normal laboratory ranges.[6] A small portion of patients with inflammatory enteric neuropathy includ-

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ing IBS, had antibodies directed towards neuronal ion channels in immunochemical analysis of full-thickness jejunal laparoscopic biopsies.[7] Only 2 of 33 patients, both with IBS, were found to have positive antibody titers. One had autobodies to voltage-gated potassium channels and one had antibodies to α3-acetylcholine receptor.[7] And the prevalence of serum neural autoantibodies with IBS did not differ significantly from controls.[8] To date, the specific blood parameter for IBS has not been identified.

Lembo et al[9] reported that complex patterns of the serum concentration among 10 biomarkers were identified that best separated IBS from non-IBS in a training cohort of patients (n = 1,205) using the Smart Diagnostic Algorithm. The sensitivity and specificity of the 10-biomarker algorithm for differentiating IBS from non-IBS was 50% and 88% respectively. The positive predictive value was 81%, and the negative predictive value was 64% at 50% IBS prevalence in the validation cohort. But the biomarkers were not directly involved in the IBS pathophysiology.

The main finding in the present study was the prevalence of higher levels of GnRH IgM antibodies in patients with idiopathic GI complaints in the form of IBS or dysmotility. There was no correlation to the presence of these antibodies and any laboratory analyses or other co-existing diseases. The GnRH and its receptor were present in the human enteric nervous system (ENS).[4,10] The GnRH effect on the ENS is not completely evaluated, but GnRH has been shown to stimulate motor function in the GI tract in female rats,[11] and to stimulate motor function in a patient suffering from chronic intestinal pseudo-obstruction.[12] Antibodies against GnRH and reduced amount of GnRH containing neurons in the ENS have sporadically been found in patients suffering from IBS.[4] The antibodies may be secondary to damage of the ENS exposing GnRH to immune-reactive cells, eg, mast cells, resulting in neuronal degeneration.[13] But, little is known about the relation in the development of the antibodies and any dysmotility symptoms, yet. Although the role of GnRH antibodies is not fully understood, there is a possibility that the antibodies may be a kind of functional antibody in pathophysiology of motility disorder.

In present study, antibodies against GnRH are the first objective specific blood parameters found so far. But this study considered all antibody levels above 0 as positive expression, and if a higher baseline of antibodies present in serum had been regarded as positive expression, almost all controls would have been below this level. Therefore, the cut off level for positive expression of GnRH IgM antibodies should be investigated. In spite of this limitation, this article has provided an interesting insight into an autoimmunity in pathogenesis of IBS and dysmotility in distinction from various autoimmune response with IBD and celiac disease. The physiologic and pathophysiologic role of GnRH on GI functions deserves further study.

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