

Celiac Disease, Gut-Brain Axis, and Behavior: Cause, Consequence, or Merely Epiphenomenon?

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The classic view of celiac disease as a gastrointestinal disorder of childhood has radically changed in the past few decades thanks to a better understanding of its pathogenesis. Celiac disease is now considered an autoimmune enteropathy triggered by the ingestion of gluten-containing grains in genetically susceptible individuals.¹ Although the gastrointestinal tract is the target of the autoimmune insult, celiac disease is a systemic disease, and its presentation can involve any organ or tissue of the body.^{1,2} One of the most fascinating yet poorly understood clinical presentations of celiac disease involve changes in behavior, including short-term memory loss, anxiety, depression, sleep disturbances, cognitive impairment, psychosis, and attention-deficit disorder.³ The degree to which these symptoms are the consequence of having a chronic disease versus celiac disease itself has not been clear. In this issue of *Pediatrics*, however, Smith et al provide evidence suggesting that celiac disease may in fact be the cause of these behavioral problems.⁴ By assessing the psychological functioning of infants enrolled in the Environmental Determinant of Diabetes in the Young trial and followed prospectively, the authors reported that 3.5-year-old children affected by celiac disease autoimmunity (CDA), defined as positive serology in children at risk, have increased reports of depression/anxiety, aggressive behavior, and sleep disturbances. Interestingly, these symptoms were significantly

greater in the 66 children with CDA whose mothers were unaware of the diagnosis compared with the 440 children with CDA whose mothers were aware of the diagnosis and the 3651 children without CDA, decreasing the chance that the reported behaviors were biased by families' subjective assessment. However, when older children (4.5 years of age) were reassessed, no relationship between CDA and psychological symptoms was detected, casting some doubts on this interpretation. An alternative explanation offered by the authors is that younger children with limited verbal skills express their physical discomfort with behavioral changes, whereas at later age, they are capable to effectively communicate their symptoms. Although plausible, this interpretation does not take into account that behavioral changes are described as possible clinical manifestations of celiac disease and sometimes as the only presenting symptoms of celiac disease in older children and adult patients,³ in some cases seriously affecting their lifestyle.⁵

The pathophysiological explanation of why patients with celiac disease can experience psychological symptoms remains a subject of debate. Two not necessarily mutually exclusive explanations suggest that (1) undigested gluten fragments structurally similar to endorphins ("gliadorphins") cross the gut barrier and the blood-brain barrier to interact with endorphin receptors, causing changes in behavior or (2) undigested

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gluten fragments activate immune cells that in turn migrate to the brain, causing neuroinflammation and ultimately behavioral symptoms.⁶ A similar interpretation has been advocated for those children affected by autism spectrum disorders responding with improvement of their behavior to the implementation of a gluten-free diet.⁷ Either way, gluten seems to be the key triggering factor for the onset of psychological disturbances as it is for any other symptom experienced by celiac disease patients.

The article from Smith et al also seems to be at odds with this paradigm because these authors reported that neither the implementation of the gluten-free diet nor the antitissue transglutaminase antibody titers were associated with changes in psychological symptoms.⁴ This apparent dichotomy can be reconciled by the consideration that in younger children, it is difficult to distinguish between those children who experience behavioral changes as an integral part of their celiac disease clinical presentation versus those children in whom psychological changes represent the somatization of pain and discomfort caused by the celiac disease-associated chronic inflammatory process or

by other factors unrelated to celiac disease. Without stratification of these 2 groups, it is conceivable that 2 variables such as the gluten-free diet and serology markers lose statistical power. No matter how the data are interpreted, celiac disease remains one of the most fascinating paradigms of the 2-way gut-brain axis cross-talk in which the combination of neuroendocrine signaling pathways, inflammatory processes, and the ecosystem (microbiome) of the gastrointestinal tract can highly influence brain functions.^{8,9} Prospective studies such as that reported by Smith et al may be a key approach to shedding light on how intestinal factors can influence human behavior and to identifying possible targets to ameliorate psychological symptoms caused by inappropriate gut-brain cross-talk.

ABBREVIATION

CDA: celiac disease autoimmunity

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