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Case 14-2016: A 37-Year-Old Woman with Adult-Onset Psychosis

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PRESENTATION OF CASE

Dr. Maureen M. Leonard: A 37-year-old woman was admitted to a psychiatric hospital for adult-onset psychosis.

The patient had been healthy and studying for a doctoral degree when she began having symptoms of psychosis. Her first symptom was a belief that "people were talking about her" as part of a larger "conspiracy" in which family, friends, and random people were part of a "game" and acting out "scenes" for her. She had had stress associated with her schooling and had contemplated changing schools. However, she had not had other symptoms of anxiety or depression, neurovegetative symptoms, or auditory or visual hallucinations.

A few months later, the patient's apartment was burglarized and vandalized; her parents were the only other people with a key, and she believed they were involved. Because of threats she made against family members, she was admitted to an inpatient state psychiatric facility. A diagnosis of psychotic disorder, possibly paranoid schizophrenia, was rendered.

An evaluation for causes of the disorder revealed evidence of marked iron-deficiency anemia, including an iron level of 18 μ g per deciliter (3 μ mol per liter; reference range, 45 to 182 μ g per deciliter [8 to 33 μ mol per liter]), a ferritin level of 6 ng per milliliter (reference range, 11 to 306), and a transferrin saturation of 3.7% (reference range, 11.0 to 50.0). The evaluation also revealed vitamin deficiencies, including a vitamin B₁₂ level of 167 pg per milliliter (reference range, 182 to 803) and a vitamin D₂ level of 10 ng per milliliter (reference value, >32).

Before admission to the state psychiatric facility, the patient had had no history of psychiatric disease. She had a remote history of a left-foot fracture and had undergone a right oophorectomy at 17 years of age for torsion of the ovary. She took no medications. Her mother recalled her being a "perfectionist," especially during her late teenage years. The patient had reported an unintentional weight loss of 9 kg over an unspecified period of time, despite self-described polyphagia and some hair thinning. She did not have diarrhea. There was no history of head injury or seizure, menopausal symptoms after the oophorectomy, or social withdrawal. Her mother had systemic lupus erythematosus, her sister had hypothyroidism

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and hyperparathyroidism, her maternal grandfather had diabetes, and an aunt had breast cancer. There was no family history of psychiatric disease.

The patient had been previously employed in human resources and had lived alone. She had traveled to the southern United States, coastal Massachusetts, and New York City but not abroad. She followed a pescatarian diet that included dairy foods and an egg daily as part of a lunch salad. She drank one alcoholic beverage per month, did not smoke cigarettes but had used marijuana, and drank two caffeinated beverages daily.

After a 1-month inpatient stay at the state psychiatric facility, the patient was discharged. Her medications included risperidone, sertraline, ferrous sulfate, calcium, vitamin D, vitamin C, and a multivitamin. At a routine follow-up visit 6 weeks after discharge, the patient was evaluated by an internist at her primary care physician's office, who found her to be excessively thin.

On examination, a thyroid nodule was identified, which prompted consultation with an endocrinologist. A biopsy of the nodule was performed, and examination of the biopsy specimen revealed evidence of Hashimoto's thyroiditis and papillary thyroid carcinoma. Radioactive iodine ablation was suggested, but the patient opted for total thyroidectomy. After the thyroid surgery and despite the administration of escalating doses of oral levothyroxine, the patient's thyrotropin level reportedly remained high (value not available) and the free thyroxine level was 0.73 ng per deciliter (9 pmol per liter; reference range, 0.80 to 1.80 ng per deciliter [10 to 23 pmol per liter]). Several weeks later, after further dose escalation of levothyroxine, the free thyroxine level was 0.80 ng per deciliter (10 pmol per liter).

A limited follow-up examination that was performed by the endocrinologist 6 months after the initial consultation revealed a height of 167.6 cm, a weight of 45 kg, and a body-mass index (the weight in kilograms divided by the square of the height in meters) of 16.1. The patient was afebrile and had a regular pulse of 75 beats per minute and a blood pressure of 90/60 mm Hg. The thyroidectomy scar was well-healed, and the remainder of the examination was reportedly normal. However, the patient's psychiatric symptoms were believed to be poorly controlled by antipsychotic medications, and it was unclear whether her thyroid conditions were related to her psychosis.

Diagnostic tests were performed, and the patient presented to this hospital for further evaluation.

DIFFERENTIAL DIAGNOSIS

Dr. Helen K. Delichatsios: In this previously healthy 37-year-old woman, psychotic symptoms developed over the course of several months. Psychiatric conditions often develop during early adulthood, and this patient presented with a relatively late onset of psychotic symptoms; therefore, we first must consider whether her psychosis is a primary psychiatric disorder or is due to an underlying medical condition. There is no family history of psychiatric illness, which argues against a diagnosis of a primary psychiatric disorder. This patient also has multiple other disorders - including iron-deficiency anemia, deficiencies in vitamins $\boldsymbol{B}_{\!_{12}}$ and D, papillary thyroid cancer, autoimmune thyroiditis, and clinically significant weight loss — that need to be considered in formulating a differential diagnosis.

IRON AND VITAMIN DEFICIENCIES

Do this patient's iron and vitamin deficiencies help to explain her psychosis? Her diet was described as pescatarian and included fish, dairy, eggs, and infrequent alcohol consumption. We do not know whether she regularly consumed fruits and vegetables, so she may have had gaps in her nutritional intake.

This patient had marked iron-deficiency anemia (iron level, 18 μ g per deciliter; ferritin level, 6 ng per milliliter), which is not unusual in a menstruating woman. We do not have information about whether she had heavy menses. Depending on her fish consumption, her dietary iron intake may not have been adequate. However, iron deficiency alone would not cause her psychosis.

This patient also had vitamin B_{12} deficiency (vitamin B_{12} level, 167 pg per milliliter). This degree of deficiency can be seen in vegetarians or persons who do not have a regular source of dietary vitamin B_{12} . Despite the patient's young age, I would consider the diagnosis of pernicious anemia and check an intrinsic-factor level. Al-

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though vitamin B_{12} deficiency can cause neurologic symptoms such as paresthesias, balance disorders, and confusion, it generally does not cause psychosis.¹

There is disagreement about the blood 25hydroxyvitamin D level that constitutes a vitamin D deficiency, but this patient's level of 10 ng per milliliter was low according to any criteria.^{2,3} Low blood 25-hydroxyvitamin D levels are not uncommon in the northeast United States, especially during the winter months. Low vitamin D levels have been associated with psychosis.⁴ However, vitamin D deficiency has been associated with many other conditions, and it is unclear whether it is the primary cause of these conditions. Although I doubt vitamin D deficiency is the sole cause of this patient's psychosis, it may be a contributing factor and therefore remains a consideration in this case.

On occasion, a patient may present with low levels of all three of these micronutrients (iron, vitamin B₁₂, and vitamin D). For example, after bariatric surgery, it is not uncommon for these deficiencies to develop and require lifelong monitoring and supplementation.⁵ The presence of multiple vitamin and mineral deficiencies raises concern about an impairment of absorption, which may lead to other nutrient deficiencies. Additional vitamin deficiencies associated with psychiatric and neurologic symptoms include vitamin B₁ (thiamine) deficiency, which can cause Wernicke's encephalopathy; vitamin B, (niacin) deficiency, which can cause pellagra; and vitamin B₆ (pyridoxine) deficiency, which can cause weakness and difficulty walking.6,7 Although we do not know the blood levels of these vitamins in this patient, it is unlikely that any of these vitamin deficiencies would adequately explain her psychotic symptoms.

WEIGHT LOSS

In addition to having nutritional deficiencies, this patient presented with weight loss. She was described as a perfectionist by her mother, and this trait has been associated with the diagnosis of anorexia nervosa. An unintentional weight loss of 9 kg over an unspecified period of time is worrisome, and cancer should be included in the differential diagnosis. No imaging studies are available in this case, but I would recommend performing magnetic resonance imaging of the head to rule out a primary brain cancer or metastatic tumor. The patient had self-described polyphagia, which makes anorexia nervosa unlikely but bulimia possible.

THYROID DISEASE

The patient reportedly noted hair thinning. Weight loss, polyphagia, and hair thinning are suggestive of an endocrine condition, such as hyperthyroidism, which can cause psychosis. Severe hypothyroidism is also associated with psychosis, but the weight loss and polyphagia argue against this diagnosis.

During the course of this patient's illness, an astute internist found her to be excessively thin and identified a thyroid nodule on palpation. Subsequent examination of a biopsy specimen revealed evidence of Hashimoto's thyroiditis (autoimmune thyroiditis) and papillary thyroid cancer. These findings are more likely to be incidental than part of the underlying process that is causing the psychosis. Thyroid nodules are very common and more likely to be detected on palpation in a thin person than in a person who is not so thin. Papillary thyroid cancer is not uncommon and would not explain the psychosis and weight loss. A separate diagnosis of autoimmune thyroiditis would not be surprising in this case, given the patient's family history. However, the autoimmune condition should assume a prominent role in narrowing the differential diagnosis for psychosis in this case.

After the thyroidectomy and despite the administration of escalating doses of levothyroxine, the patient's thyrotropin level remained high. The absorption of levothyroxine is nearly 100%,⁸ so the inability to normalize the thyrotropin level despite the administration of escalating doses of levothyroxine suggests impaired absorption. The patient took iron and calcium supplements and sertraline, agents that may delay or impair absorption of levothyroxine.^{9,10} However, escalating doses of levothyroxine should be able to overcome these medication effects.

The patient's psychiatric symptoms were also poorly controlled despite the appropriate antipsychotic medications. This is not particularly surprising, because her psychiatric condition is likely to be secondary to an underlying medical condition. As with levothyroxine, the psychiatric medications may not have been properly ab-

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sorbed. Taken together, these clues may point us toward disorders associated with malabsorption.

THYROID DISEASE, AUTOIMMUNITY, AND MALABSORPTION

Although this patient did not have any gastrointestinal symptoms, we have ample evidence to suggest that she may have had impaired absorption of micronutrients and several medications. She also had thyroid cancer, which I suspect was an incidental finding and probably unrelated to her psychotic symptoms. However, the finding of Hashimoto's thyroiditis and the subsequent inability to absorb levothyroxine after thyroidectomy are pivotal elements in shaping my thinking about a possible cause of her psychosis. The patient's family history of autoimmune disorders and development of autoimmune thyroiditis point us toward disorders associated with autoimmunity. The combination of malabsorption and autoimmunity strongly suggests the possibility of celiac disease, which is not always associated with gastrointestinal symptoms. Malabsorption associated with celiac disease would account for most if not all of the key features in this case, including the vitamin deficiencies, poor response to levothyroxine, autoimmune thyroiditis, and weight loss. Finally, although neurologic and psychiatric symptoms of celiac disease are not widely recognized, they have been reported^{11,12} and would account for the patient's adult-onset psychosis.

In order to establish the diagnosis of celiac disease, I would perform blood testing for IgA tissue transglutaminase antibodies and with a celiac disease–specific panel. I would also consider referral to a gastroenterologist for endoscopy and possible biopsy.

Dr. Eric S. Rosenberg (Pathology): Dr. Deans, would you tell us your impression when you evaluated this patient at an outpatient psychiatric clinic after she had been discharged from the state psychiatric facility?

Dr. Emily C. Deans (Psychiatry): When I initially evaluated this patient, I considered the possibility of an affective disorder, major depression, and bipolar disorder with psychosis. She did not present with any mood symptoms, so a primary mood disorder was ruled out. Schizophrenia was considered, but the onset of schizophrenia typically occurs in patients who are younger than this one. Although there is a second peak of schizophrenia onset at menopause, this patient was not yet menopausal. She did present at the peak age for the onset of a delusional disorder, which is a psychotic disorder with primary delusions. This disorder tends to occur at approximately 35 years of age and is fairly common. Many patients with delusional disorder do not seek medical care, and when they do, they often have a poor response to antipsychotic medications. Delusional disorder is characterized by isolated false, fixed beliefs and is not associated with some of the problems of cognitive and executive function that are seen in patients with other psychotic disorders, such as schizophrenia and bipolar disorder. The diagnosis of a delusional disorder fits well with the features of this patient's presentation. Some of her delusions involved her going on hunger strikes because she thought the hunger strikes would stop the conspiracy against her. This type of delusion would result in rapid weight loss and perhaps long-term nutritional deficiency. However, a delusional disorder is a diagnosis of exclusion; therefore, underlying medical conditions that could cause her psychosis should be ruled out.

DR. HELEN K. DELICHATSIOS'S DIAGNOSIS

Celiac disease complicated by psychosis.

CLINICAL DIAGNOSIS

Delusional disorder.

DISCUSSION OF MANAGEMENT

Dr. Rosenberg: Dr. Leonard, would you tell us what happened next with this patient?

Dr. Leonard: On the basis of testing performed by the patient's endocrinologist, celiac disease was considered to be the cause of a malabsorption syndrome; it accounted for the patient's anemia, weight loss, vitamin deficiencies, and poor response to levothyroxine. The diagnostic standard for celiac disease is a biopsy of the small intestine. Serologic tests — including tests for IgA tissue transglutaminase antibodies, endomysial antibodies, and deamidated gliadin peptide antibodies — help to identify persons who may benefit from duodenal biopsy.¹³ General consensus regarding these studies is that

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the test for IgA tissue transglutaminase antibodies is the most reliable and cost-effective; the test was performed in this patient and was strongly positive at 179 U per milliliter (reference value, <20).

Next, the patient was referred to a gastroenterologist for further evaluation for possible celiac disease. The gastroenterologist performed esophagogastroduodenoscopy with small-bowel biopsy. Pathological examination of the biopsy specimen reportedly confirmed the diagnosis of celiac disease.

After receiving the diagnosis of celiac disease, the patient thought her practitioners were being deceitful regarding the diagnosis and refused to adhere to a gluten-free diet. Psychotic symptoms and paranoia persisted, and she continued to "find clues" of conspiracy against her. She lost her job, became homeless, and attempted suicide; her family took out a restraining order against her. Eventually, she was rehospitalized at a psychiatric facility, where she was placed on a glutenfree diet.

After nearly 3 months at the psychiatric facility, the patient's delusions dissipated. She was discharged on a strict gluten-free diet and was taking risperidone daily. At that time, she sought the opinion of the celiac center at this hospital to determine whether her psychiatric symptoms could be related to celiac disease.

When we evaluated the patient at this hospital, our goal was to determine whether she had celiac disease, and if so, to determine whether her psychiatric symptoms were related to this diagnosis. Celiac disease should be considered in patients with gastrointestinal symptoms and in patients with extraintestinal problems, such as iron-deficiency anemia that is unresponsive to treatment, arthritis, or elevated levels of liver enzymes; it should also be considered in highrisk patients, including those with a family history of celiac disease, those with type 1 diabetes mellitus, and those with autoimmune thyroid disease.14 This patient had gastrointestinal involvement that was manifested by weight loss and had evidence of malabsorption (deficiencies in vitamins D and B_{12} ; she also had iron-deficiency anemia that was unresponsive to therapy, one of the most common extraintestinal manifestations seen in adults presenting with celiac disease. Furthermore, her recent diagnosis of Hashimoto's thyroiditis placed her in a high-risk group for celiac disease, thus indicating that screening should be considered. The first step in her evaluation when she presented to this hospital was to review the biopsy specimen of the small bowel that had been obtained by the gastroenterologist.

PATHOLOGICAL DISCUSSION

Dr. Vania Nosé: Review of the duodenal-biopsy specimen obtained by the gastroenterologist showed histologic changes involving the villi, crypts, enterocytes, and lamina propria (Fig. 1A). The duodenal mucosa showed moderate-tomarked villous blunting and atrophy. The surface epithelial cells appeared cuboidal or flattened, and a few goblet cells, attenuation of the brush borders, cytoplasmic basophilia, loss of polarity, and loss of the basal nuclear orientation were present. There was an increased number of intraepithelial lymphocytes in the surface epithelium and associated lymphoplasmacytosis in the lamina propria. More than 40 intraepithelial lymphocytes over 100 surface enterocytes were seen.

Immunostaining for CD3 revealed an increased number of intraepithelial and lamina propria lymphocytes (Fig. 1B), and immunostaining for CD8 revealed an increased number of intraepithelial lymphocytes (Fig. 1C). There was marked crypt hyperplasia with elongation of the crypts and an expanded proliferative zone of the crypts, as well as increased mitotic activity and a decreased number of goblet cells (Fig. 1D). Staining for Ki-67 highlighted hyperplastic crypts (Fig. 1E and 1F). The overall findings for this biopsy specimen are consistent with celiac disease (modified Marsh classification 3b).

FOLLOW-UP

Dr. Leonard: On review of the clinical history, positive serologic tests, and duodenal-biopsy specimen with villous blunting, we confirmed that the patient had celiac disease.

At the time of the patient's visit to the celiac center at this hospital, she was following a glutenfree diet; she reported and her psychiatrist confirmed that the delusions were not present. Therefore, if the symptoms were in fact related to celiac disease, the disease must have been in remission. To assess this, we repeated the sero-

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Figure 1. Initial Biopsy Specimen of the Duodenum.

Hematoxylin and eosin staining of a biopsy specimen of the duodenum shows damaged surface epithelium, numerous intraepithelial lymphocytes, and an increased number of lamina propria lymphocytes and plasma cells (Panel A). Immunostaining of the same field for CD3 shows an increased number of intraepithelial and lamina propria lymphocytes (Panel B). Similarly, immunostaining for CD8 shows an increased number of intraepithelial lymphocytes (Panel C). In addition, hematoxylin and eosin staining shows mild-to-moderate villous blunting, crypt hyperplasia, and an expanded proliferative zone of the crypts (Panel D). Immunostaining for Ki-67 shows marked proliferation in the epithelial cells of the crypts that extends to the surface epithelial cells, highlighting the expanded proliferative zone of the crypts and hyperplastic crypts (Panel E and F). Together, these findings are consistent with the diagnosis of celiac disease (modified Marsh classification 3b).

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logic test for IgA tissue transglutaminase antibodies, which was negative, and we scheduled a repeat endoscopy with duodenal biopsy. If the patient's disease were in remission, we would no longer see active villous blunting (consistent with Marsh classification 3) and would instead see healing mucosa without abnormality (Marsh classification 0) or possibly see a mild increase in the number of intraepithelial lymphocytes (Marsh classification 1) and crypt hyperplasia (Marsh classification 2).¹⁵

ADDITIONAL PATHOLOGICAL DISCUSSION

Dr. Nosé: Examination of the second duodenalbiopsy specimen, which was obtained at this hospital, showed that the duodenal mucosa had normal villous architecture. There was no villous blunting, villous atrophy, crypt hyperplasia, or increase in the number of intraepithelial lymphocytes (Fig. 2). The regression of mucosal abnormalities, with normalization of villi to a Marsh classification of 0, is considered to be a histologic remission.

ADDITIONAL DISCUSSION OF MANAGEMENT

Dr. Alessio Fasano: Extraintestinal manifestations of celiac disease may be more common than gastrointestinal manifestations, and physicians should have a low threshold to test patients for IgA tissue transglutaminase antibodies in order to establish a diagnosis of celiac disease. In this case, the astute endocrinologist connected the signs of malabsorption, the history of Hashimoto's thyroiditis, and the poor response to levothyroxine to make the diagnosis of celiac disease.

Patients with abnormal test results for IgA tissue transglutaminase antibodies or those in whom celiac disease is highly suspected must be referred to a gastroenterologist for confirmatory testing with endoscopy and biopsy. The patient must remain on a gluten-containing diet for testing to be accurate. A trial of a gluten-free diet is not appropriate unless celiac disease has been ruled out; once the patient is on a gluten-free diet, a clinician cannot distinguish between



Figure 2. Subsequent Biopsy Specimen of the Duodenum (Hematoxylin and Eosin).

A second biopsy specimen (Panels A, B, and C) shows the duodenal mucosa with normal villous architecture and no villous blunting or atrophy. There is no increase in the number of intraepithelial lymphocytes, the goblet cells are preserved, and the polarity of the nuclei is maintained. The regression of mucosal abnormalities, with normalization of villi to a Marsh classification of 0, is considered to be a histologic remission.

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Table 1. Extraintestinal Manifestations of Celiac Disease.
Neurologic: peripheral neuropathy
Dental: oral cavities, aphthous ulcers, and enamel defects
Cutaneous: dermatitis herpetiformis, eczema, psoriasis, brittle nails, and hair thinning
Cardiovascular: associated with myocarditis, blood-flow alterations, and atrial fibrillation
Pulmonary: Lane-Hamilton syndrome
Pancreatic: acute pancreatitis
Renal: increased risk of glomerulonephritis and end- stage renal disease
Reproductive: infertility, miscarriage, and delayed puberty
Hematologic: anemia
Hepatic: hepatitis
Musculoskeletal: joint pain, osteopenia, and osteoporosis
Table 2. Neuropsychiatric Symptoms Associated with Celiac Disease.

Confirmed

Loss of short-term memory
Anxiety and depression
Psychosis
Ataxia
Seizures
Irritability
Chronic headache
Possible
Autism
Attention deficit-hyperactivity disorder
Schizophrenia

celiac disease and other gluten-related disorders, including nonceliac gluten sensitivity, because both can have extraintestinal manifestations. If a patient has initiated a gluten-free diet without having had the proper testing, a genetic test may be helpful to identify whether there is a need to reintroduce gluten for confirmatory testing for celiac disease. Confirming the diagnosis of celiac disease is essential, since the diagnosis of an autoimmune disease alters a patient's future treatment.

Does this patient's psychosis fit with the di-

agnosis of celiac disease? It is not unusual for involvement of the central nervous system to lead to neurologic or psychiatric symptoms, or both. Celiac disease was classically described as a gastrointestinal condition that almost exclusively affects white children.¹⁶ Now celiac disease is described as an autoimmune disorder that can affect persons of any age or race and can involve any tissue or organ of the body (Table 1).¹⁷ The typical gastrointestinal symptoms (diarrhea, bloating, failure to thrive, and weight loss) can be easily understood by the underlying intestinal damage caused by the autoimmune attack that occurs after the ingestion of gluten, but the many extraintestinal symptoms that patients with celiac disease often have are more difficult to explain. New insights on the pathogenesis of celiac disease suggest that it is truly a systemic disease that can spread from the intestine to any tissue or organ of the body.^{12,17} One of the most intriguing yet controversial clinical presentations of celiac disease involves the nervous system as a preferred target.¹⁸ Patients with celiac disease often have chronic headache, short-term memory loss, irritability, anxiety, and depression and more rarely have seizures, ataxia, autism, attentiondeficit disorders, and psychosis (Table 2).12,18 Although we do not have a definitive explanation of the way in which an inflammatory process in the intestine affects the brain, there is growing evidence of close functional and organic interactions between these two systems, which are typically described as the gut-brain axis.¹⁹

A strict gluten-free diet is necessary to control symptoms; however, in patients with psychoses or other neuroinflammatory conditions, adherence to a gluten-free diet can be difficult. Patients with celiac disease should be monitored by a gastroenterologist and by a dietician with expertise in celiac disease and the gluten-free diet.

ADDITIONAL FOLLOW-UP

Dr. Leonard: This patient was motivated to discover whether her delusional symptoms were directly related to celiac disease. Under the care of her psychiatrist, she was weaned off the very small dose of psychiatric medication she had been taking, and she remained symptom-free for several months.

Unfortunately, during this time, the patient

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inadvertently ingested gluten. She became delusional, was hospitalized, and her level of IgA tissue transglutaminase antibodies, which had previously been normal, was again elevated. Currently, the patient's level of IgA tissue transglutaminase antibodies is persistently elevated, her anemia has returned, and she is not following a gluten-free diet because of a delusion that the diagnosis of celiac disease is incorrect.

FINAL DIAGNOSIS

Celiac disease in histologic remission.

This case was presented at Medical Grand Rounds.

Dr. Fasano reports receiving consulting fees from General Mills, Crestovo, and Pfizer and lecture fees from Mead Johnson and holding stock in Alba Therapeutics. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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