

Neurological Deficits in Patients With Celiac Disease

Adi Vaknin-Dembinsky, MD; Rami Eliakim, MD; Israel Steiner, MD

Celiac disease (CD) is an autoimmune enteropathy triggered by the ingestion of gluten in genetically susceptible individuals.¹ Developments in the understanding of the pathogenetic basis of the disease and the introduction of serological diagnostic markers have enabled the delineation of its epidemiological features and its clinical spectrum. This, in turn, has led to increased interest in the possible neurological manifestations and involvement in patients with this disorder.

CLINICAL DESCRIPTIONS

Celiac disease is clinically characterized by a malabsorption syndrome, weight loss, abdominal distention, diarrhea, steatorrhea, malaise, iron deficiency anemia, and bone disease. Most of these features were already noted in the first description of the disorder, dated 200 AD:

The stomach being the digestive organ, labors in digestion when diarrhea seizes the patient. If this diarrhea does not proceed from a slight cause of only one or two days' duration, and if, in addition, the patient's general system be debilitated by atrophy of the body, the celiac disease of a chronic nature is formed.^{2(p350)}

Digestion of the food is left "half finished. The food . . . is changed to a state which is bad in color, smell and consistence," the patient is "emaciated, atrophied and pale feeble," and his "limbs fail."^{2(p350)}

This description belongs to the Greek physician Aretaeus the Cappadocian, who wrote a medical textbook describing various conditions, including neurological abnormalities such as epilepsy, headache, vertigo, and paralysis.³ Aretaeus was also the first to use the word *celiac*, which probably means colic. However, he mistakenly thought that this disorder is more prevalent among adults, and recommended rest and fasting.

In the 17th century, the term *sprue* (nontropical sprue is sometimes used synonymously for celiac) was introduced into the English language from the Dutch word *sprouw*, which means chronic diarrhea. In 1887, the disease drew the attention of the English physician S. J. Gee, MD, who noted that children (who take the main brunt of CD) are also affected and recognized the importance of diet in the management of patients with CD. Yet, he allowed thin toasted slices of bread, and noted that, "A child who was fed upon a quart of the best Dutch mussels daily thrived wonderfully, but relapsed when the season for mussels was over. This is an experiment I have not yet been able to repeat, . . . but if the patient can be cured at all, it must be by means of a diet."⁴

In 1908, the first discussion of the disorder in the US literature appeared by Herter,⁵ and for several decades, CD was known as Gee-Herter disease.

DIETARY THERAPIES

At the turn of the century, CD was usually a fatal condition.⁶ However, the introduction of the right diet in the late 1920s and early 1930s revolutionized its prognosis. It was Haas,⁷ following a case of anorexia nervosa that he cured with a banana diet, who recommended a similar regimen for CD and reported cure in 8 of 19 such treated patients. The Dutch pediatrician Karel Dicke, MD, championed a wheat-free diet before 1940, but it is believed that he found proof for his theory

From the Department of Neurology, Hadassah University Hospital, Jerusalem (Drs Vaknin-Dembinsky and Steiner), and the Department of Gastroenterology, Rambam Medical Center, Haifa (Dr Eliakim), Israel.

during World War II when the scarcity of bread led to a decrease in the severity of CD in afflicted children. When Swedish planes dropped bread into the Netherlands, there was a quick relapse.⁸ This anecdote, however, was recently challenged by Smith,^{9(p387)} “the amount of bread that the neutral Swedes parachuted into the Netherlands during the war was . . . so small that [the possibility that] it would have reached the rare children with celiac disease in sufficient quantities to make any significant observation possible must be utterly far fetched.” The banana vs wheat-free diet was still an open issue in 1963 when Haas¹⁰ wrote that “Dicke’s demonstration was an excellent achievement . . . but clinically it was a possible disservice, since it ignored other carbohydrates and etiological factors.”

OTHER LANDMARKS

Three major landmarks in the history of CD should be noted: (1) the ability to obtain biopsy specimens from the small intestine¹¹; (2) the realization that gluten is the compound responsible for the damage to the intestinal mucosa¹²; and (3) the recent finding of antigliadin, anti-endomysial, and tissue transglutaminase antibodies (specific and sensitive markers for the disease) in the serum of patients with CD.¹³

THE NEUROLOGICAL FEATURES OF CD

Anecdotal reports on the neurological involvement in patients with CD appeared in the late 19th century, when Gibbons⁶ suggested that “this disease depends upon a functional disturbance of the nervous supply of the liver, pancreas, glands of Brunner and follicles of Lieberkuhn.” The first case description appeared in 1908 by Brown,¹⁴ who noted 2 patients with “sprue and peripheral neuritis.” This was followed in 1925 by a case report of “ataxia and anesthesia” of both legs.¹⁵

Pathological evidence for myelopathy was provided in 1927 by Reed and Ash,¹⁶ who described 8 pa-

tients with CD. A central nervous system autopsy specimen was available in 2. The first was summarized as follows:

in the light of the knowledge of the relation of symptoms to pathologic conditions in subacute degeneration of the spinal cord, this case presents indication of damage to the spinal cord which cannot be ignored. [However,] sections of the cervicodorsal cord examined . . . were normal in appearance. . . . Negative results of postmortem examination of the cord do not [however] change the fact that the cord functioned abnormally in life.^{16(p789)}

An autopsy specimen of the second patient disclosed “advanced degeneration of the lateral and posterior columns of the spinal cord” and “chronic cerebral leptomeningitis.”^{16(p793)} Using a “retrospectroscope,” this latter finding may put in question the entire diagnosis of CD in this patient. Similar myelopathic features and pernicious anemia-like findings led Elders^{15(p72)} to suggest that “sprue is a deficiency disease” and “it is difficult to accept a different aetiology for the two diseases.”

The first review of neurological involvement in patients with CD was published by Woltman and Heck¹⁷ from the Mayo Clinic, Rochester, Minn; they extensively reviewed the literature up to 1937. They concluded that “in a review of more than two hundred available articles on the subject of sprue it was found that only twenty included evidence of organic involvement of the nervous system, and some of these were attributed to electrolyte depletion.”^{17(p300)} However, this study addressed only myelopathy. Likewise, Perez-Santiago and Rubini stated in 1961 that neurological lesions are rarely, if ever, encountered in patients with CD. Cooke and Smith¹⁸ published a 36-page comprehensive series on neurological manifestations of CD. The article itself is 16 pages, but it also contains an “appendix” with extensive case reports. They concluded that it seems “from the nature and inconsistency of the pathological findings that multiple factors are concerned and that rela-

tion between steatorrhea and neuropathy is not to be explained simply as cause and effect.”^{18(p698)} Despite all the advances in the field,^{1,11-13} this statement is still valid and the pathophysiological basis of neurological impairment in patients with CD remains largely unexplained.

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Corresponding author: Israel Steiner, MD, Department of Neurology, Hadassah University Hospital, PO Box 12000, Jerusalem 91120, Israel (e-mail: isteiner@md2.huji.ac.il).

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