Level 2

Non Celiac Enteropathy
Subtitle: Damage to the Small Intestine Not Caused by Celiac Disease

Underlined words are defined in the Glossary below.

KEY POINTS:

- Villous atrophy (VA) is the characteristic microscopic finding in celiac disease (CD). However, VA is also seen in various conditions other than CD.

- VA is typically associated with intraepithelial lymphocytosis (IELs) in CD. Conditions causing a celiac-like small intestinal enteropathy with villous atrophy and lack of IELs on biopsy are collectively referred to as non celiac enteropathy (NCE).[1]

- A suggested diagnosis of NCE requires a patient to have VA and meet one of the following criteria:[1]

    - Negative CD HLA-DQ2/DQ8 gene testing.
    - Negative CD serology (normal tTG level) on a gluten-containing diet and lack of histological improvement on a gluten-free diet (GFD).
    - Negative CD serology on a gluten-containing diet along with a confident alternate diagnosis such as combined variable immunodeficiency or autoimmune enteropathy.

    Both CD and NCE can be clinically 'silent;' however, classic symptoms for CD including diarrhea, weight loss, abdominal pain and fatigue as well as vitamin B12 and folate deficiency can occur in either one and are of little use in differentiating between disorders. Similar to gastrointestinal symptoms, symptomatic response to a GFD is also not a specific test for CD and may be seen in NCE. Symptomatic response to a GFD does not represent intestinal healing or differentiate reliably between NCE and CD and should not generally be used as a diagnostic feature.[1]

Various conditions causing NCE with villous atrophy include:

Common variable immunodeficiency (CVID): CVID is the most common symptomatic primary immunodeficiency in adults. Symptoms of CVID are usually mixed and nonspecific. It commonly occurs among children (1-5 years) and young adults (18-25 years). [2]

- The main clinical manifestations are recurrent infections present in the respiratory tract, gastrointestinal (GI) tract, skin, and soft tissues. Involvement of the GI tract with or without malabsorption, autoimmunity, lymphoma or other malignancies can also occur. Virtually 60% of patients with CVID present with diarrhea and 10% develop digestive complications such as idiopathic malabsorption associated with weight loss.
- CVID-related enteropathy is a celiac-like illness with villous atrophy and crypt hyperplasia seen on a biopsy but showing no improvement on a GFD. Below normal serum levels of IgG, IgA and/or IgM are observed in CVID.
- Antibiotics, vaccination, immunosuppressants and long term intravenous immunoglobulins are the primary methods of therapy in patients with CVID.

Collagenous sprue: Collagenous sprue occurs predominantly in older adults. It is closely linked to CD. [3, 4]

- Clinical manifestations include persistent diarrhea, progressive weight loss, and severe malabsorption causing multiple nutrient deficiencies that fail to respond to the GFD. Similar to CD, small bowel ulceration, perforation and lymphoma may complicate the clinical course of collagenous sprue.
- Collagenous sprue is characterized by histological evidence of increased sub-epithelial collagen deposits in addition to villous atrophy. Collagen deposits may also occur in mucosal sites in the stomach or colon, or both, at the same time.
- Treatment depends on the presence or absence of symptoms and the severity of symptoms. In the asymptomatic stage, no treatment is required. Oral mesalamine and budesonide are commonly prescribed medications.

Crohn's disease: Crohn's disease is the second most common cause of villous atrophy after CD.[5]

- Chronic diarrhea with blood or mucus in the stools, weight loss, abdominal pain, and fever are typical symptoms. Extra intestinal manifestations include arthritis, liver disease such as primary sclerosing cholangitis, skin, eyes, and lung involvement.
- Elevated sedimentation rate on blood test and on biopsy by endoscopy reveals granulomatous inflammation of the intestine in addition to villous atrophy, especially in the terminal ileum (lower section). . Multiple levels of small and/or large intestine can be involved.
- Treatment with corticosteroids or mesalamine or immunomodulators is involved depending upon the extent and severity of disease.

Autoimmune enteropathy (AIE): AIE is an infrequent cause of malabsorption. This disease is more frequent in children. [6, 7]

- Symptoms of AIE can be quite debilitating, including both intestinal and extra- intestinal manifestations. Individuals generally have uncontrollable diarrhea with malabsorption and anorexia leading to severe weight loss that requires treatment with total parenteral nutrition. Patients with AIE may have a history of autoimmune conditions.
- Special type of antibodies called anti-enterocyte antibodies in the blood are seen in AIE. In addition to the microscopic findings seen in CD, distinct features called crypt apoptotic bodies found in AIE help in differentiating CD from AIE. Some patients may also have IgA deficiency.
- A trial of oral nutritional supplementation may be successful. However, for many patients with AIE, total parenteral nutrition is required. In addition, medical therapy is commonly used, most typically with corticosteroids (budesonide and prednisone) or immunosuppressive therapy when no response to corticosteroids is seen.

Post viral enteropathy: This is an acute, self limiting illness followed by an episode of viral gastroenteritis. Stool studies and other investigations are unrevealing.

- Symptoms are nonspecific and typically less severe.
- VA may sometimes be present but is quickly resolved.
- Temporary avoidance of certain foods (eg: dairy, carbohydrate-rich or high fatty foods) that worsen the symptoms is sometimes beneficial.

Immune mediated enteropathy: Also called “Sprue-like intestinal disease” or “unclassified sprue” is a “wastebasket” disease diagnosis that appears to represent a mixed group of different disorders with no specific identified cause. It is a diagnosis of exclusion.[8]

- Persistent symptoms (diarrhea, weight loss, abdominal pain) and changes in the small bowel biopsies are present despite a strict GFD. A history of autoimmune conditions may be present.
- Isolated deficiency of serum IgG or IgM may be present. Chronic immune mediated damage to the small intestine without specific findings is seen.
- Most patients respond to treatment with immunosuppressive therapy.

Drug induced enteropathy/Medication-related enteropathy: Villous atrophy can result from taking certain medications for other medical conditions. [9, 10]

- Omlesartan and non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, aspirin etc., are found to be associated with varying degrees of villous atrophy.[9, 10]
- Symptoms improve upon discontinuation of the medication. Follow-up biopsy is not needed.
- Assuming that celiac disease has been ruled out, if you have tried the GFD to see if it helps with the above symptoms, you can resume a gluten containing diet as gluten is not the cause of the symptoms in this case.

Eosinophilic gastroenteritis (EG): It is an uncommon disorder of the GI tract affecting both children and adults. The majority of cases of EG are reported in whites, with some cases occurring in Asians. The majority of the cases clinically present in males between 30-50 years.[11]

- Symptoms include abdominal pain, weight loss, vomiting and diarrhea. Severity of the symptoms depends on the site and the layer of the GI tract involved. Patients most often have a history of multiple allergies.
- Elevated eosinophils in blood are usually seen. Elevated serum IgE levels are seen especially in children with history of food intolerance or allergy. In addition to VA, infiltration of the different layers of GI tract with eosinophils is the characteristic feature of EG on intestinal biopsies. However, intestinal infection by parasites and other causes of intestinal eosinophilia have to be ruled out before arrive at the diagnosis of EG.
- A dietary intervention, such as an elimination diet, is recommended particularly when a history of food intolerance or allergy is reported. Oral corticosteroids are the most frequently used therapy for EG.

Peptic Duodenitis: It is the inflammation of the duodenum secondary to acid-related damage which is often induced by medications such as NSAIDs and corticosteroids, or helicobacter pylori infection.[12]

- Symptoms include abdominal pain or discomfort, nausea, and vomiting. A history of peptic ulcer disease or symptom improvement with acid suppressive therapy is a diagnostic clue for peptic duodenitis.
- In biopsy specimens showing intraepithelial lymphocytosis and VA, prominent neutrophilic inflammation is the characteristic feature of peptic duodenitis.
- Treatment involves discontinuation of medicines causing the damage, initiation of acid suppressive medications, and treatment of helicobacter pylori, if detected.

Small Intestinal Bacterial Overgrowth (SIBO): SIBO results when protective bacteria are compromised and harmful bacterial overgrow in the first portion of the small intestine. These harmful bacteria are normally restricted to the colon. Certain situations that reduce the number of protective bacteria include exposure to antibiotics, decreased stomach acid secretion, diminished digestive enzyme production, gastrointestinal obstructions, etc. Any inflammation of the gastrointestinal tract including CD can increase the risk of SIBO.

- SIBO is a common cause of chronic diarrhea. Bloating, gas and abdominal pain are other symptoms. If left untreated, SIBO can lead to malabsorption and malnutrition.
- More than 50% of the time, biopsies are normal in patients with SIBO. Sometimes, only villous blunting may be seen in severe, untreated cases and absence of intraepithelial lymphocytosis helps in differentiating SIBO from CD.

- Proper antibiotic therapy aimed to restore the normal gut flora is the treatment for SIBO.

For more information on SIBO, please refer to the SIBO articles under "Nutritional Considerations on the Gluten-Free Diet" on www.celiacnow.org.

TAKE HOME MESSAGES:

1. Although CD is the most common cause of duodenal villous atrophy, NCE is not rare and may easily be mistaken for CD.
2. NCE is suggested by a normal initial tTG level, lack of characteristic features of CD on biopsy, and lack of histologic response to a GFD.
3. Subjective response to the GFD by itself is a poor indicator for CD.
4. NCE can often be confirmed by negative HLA-DQ2/DQ8 gene testing; targeted investigations can determine a definitive etiology in most cases and facilitate effective treatment.

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Author: Rohini Vanga MD
Editors: Melinda Dennis, MS, RD, LDN and Daniel Leffler MD

Glossary:

Crypt apoptotic bodies: a group of dead cells surrounded by a sealed membrane formed within the gland called crypt which is found in the intestinal lining

Crypt hyperplasia: increased growth of the crypt which is a gland found in the epithelial lining of the small intestine and colon

Eosinophil: white blood cells; one of the immune system components responsible for combating certain parasites and infections

Extra intestinal: Situated or occurring outside the intestines

Granulomatous: a special type of inflammation that can occur in a wide variety of diseases. Granuloma is a collection of tiny immune cells known as macrophages.

Histologic: microscopic anatomy of cells and tissues by examination under microscope

Idiopathic: an adjective used primarily in medicine meaning arising spontaneously or from an obscure or unknown cause

IgA deficiency: lack of immunoglobulin A (IgA), a type of antibody that protects against infections of the mucous membranes lining the mouth, airways, and digestive tract

Immunomodulators: active agents or substances that are administered in the treatment of certain diseases by inducing, enhancing, or suppressing an immune response

Immunosuppressant: a substance that reduces the activation or efficacy of the immune system

Intraepithelial lymphocytosis: deposits of a specific type of white blood cells within the lining of the GI tract

Intravenous immunoglobulins: a blood product that is administered through the veins

Lymphoma: a type of blood cancer that occurs when B or T lymphocytes, the white blood cells that form a part of the immune system and help protect the body from infection and disease, divide faster than normal cells or live longer than they are supposed to

Neutrophilic: accumulation of a special type of white blood cells called neutrophils that fight against infections. These cells are an important part of your immune system.

Primary Sclerosing Cholangitis: a disease of the bile ducts that causes inflammation and subsequent obstruction of bile ducts both at intrahepatic (inside the liver) and extrahepatic (outside the liver) level.

Sedimentation rate: rate at which red blood cells deposit in a period of one hour. It is a common blood test, and is a non-specific measure of inflammation.

Sub-epithelial collagen deposits: Collagen is a naturally occurring protein that is deposited beneath the epithelial layer of the body.

Total Parenteral Nutrition: feeding a person intravenously, bypassing the usual process of eating and digestion. The person receives nutritional formula that contains nutrients such as glucose, amino acids, lipids, and added vitamins and minerals.

Viral gastroenteritis: inflammation of the lining of the stomach, small intestine, and large intestine. Several different viruses can cause viral gastroenteritis, which is highly contagious and extremely common. The main symptoms of viral gastroenteritis are watery diarrhea and vomiting. Dehydration is the most common complication of viral gastroenteritis.