Non Responsive Celiac Disease

Key Points

- Currently, the only treatment for celiac disease (CD) is strict life-long adherence to a gluten-free diet (GFD). A minority of cases, however, will fail to completely improve or may relapse while on the diet.\(^1\)

- Non responsive Celiac Disease (NRCD) affects 7-30% of patients on a GFD.\(^2\) It may be defined as continued signs and symptoms that suggest CD despite dietary gluten avoidance for 6-12 months.\(^3\)

- NRCD can be further classified as primary or secondary. Primary refers to an initial failure to achieve symptomatic response on a GFD. Secondary NRCD occurs when symptoms return while on a GFD.\(^2\)

- When the symptoms fail to improve or recur, proper evaluation should be followed to identify and treat the specific cause (See Figure 1).\(^4\) It is important to review and carefully examine the initial diagnosis of CD based on the history of symptoms, signs, lab tests, and biopsy results at the time of diagnosis.

- An endoscopy should be considered if the diagnosis was done based only on blood tests. This will also help the doctor assess intestinal healing and other conditions that can cause similar biopsy findings (See Blood Tests and Endoscopy).

- The most common cause of NRCD is accidental gluten ingestion. Gluten exposure accounts for 35-50% of ongoing symptoms in patients with CD.\(^3\) For this reason, it is very important to obtain sound dietary advice from an expert celiac dietitian.\(^1\) It will also help you identify if the cause of ongoing symptoms could be due to lactose intolerance or fructose malabsorption. These two conditions can occur as a result of intestinal damage caused by CD.

- A positive blood test for CD could be helpful to assess cross-contact with gluten and adherence to the GFD. It is important to remember, however, that a normal blood test does not exclude cross contact with gluten as a possibility.

- After a dietitian carefully excludes gluten as a cause of the symptoms, a small intestinal biopsy may be repeated and compared with the initial biopsy. A normal or near normal biopsy will lead the doctor to consider other possible causes (See Table 1).\(^5\)

- It is widely accepted that small intestinal villous atrophy (decrease in size, or wasting) is required for the diagnosis of CD.\(^1\) Biopsies of the small intestine are obtained with the help of a safe and
quick procedure called an esophago-gastro-duodenoscopy (EGD) or endoscopy.

- An endoscopy is routinely used to evaluate gastrointestinal symptoms and allows direct visualization of the upper gastrointestinal tract (esophagus, stomach, beginning portion of the small intestine called the duodenum) through a flexible, narrow tube with a camera attached at the end called an endoscope. The endoscope is inserted through the mouth and moved through the stomach into the duodenum.

Other causes for NRCD include but are not limited to:

1. **Small intestinal bacterial overgrowth syndrome (SIBO):**
   - Small intestinal bacterial overgrowth syndrome (SIBO) is caused by abnormal intestinal motion, lowered immune defenses, or damage to the intestinal mucosa. These factors create imbalance in the gut flora that results in overgrowth of the harmful bacteria.
   - This condition can be challenging but is often assessed with a hydrogen and methane breath test and treated with a course of antibiotics. The use of prebiotics and probiotics may also be useful.

2. **Microscopic colitis:**
   - Microscopic colitis is a common cause of long standing diarrhea caused by inflammation of the large intestine (colon).
   - It generally presents with episodes of watery, non-bloody diarrhea of long standing, intermittent, or recurrent course. 
   - The diagnosis is made by colonoscopy and confirmed by assessment of biopsies under a microscope (thus the name microscopic).
   - Treatment varies depending on the persistence and severity of symptoms.

3. **Pancreatic insufficiency:**
   - Pancreatic insufficiency is caused by insufficient production of digestive enzymes by the pancreas. This low production leads to malabsorption of nutrients and fatty diarrhea (pale, bulky and foul smelling stools, often with oil droplets).
   - Diagnosis is made by measuring the amount of enzymes (usually elastase) and/or fat in the stool.
   - Treatment is based primarily on pancreatic enzyme replacement therapy. It may also include lifestyle modifications and vitamin supplementation.

4. **Irritable bowel syndrome (IBS):**
   - IBS is a functional disorder of the intestine that commonly presents with abdominal pain or discomfort, is associated with bowel changes and is usually relieved by bowel movements. Other symptoms such as bloating, diarrhea and/or constipation are required to establish a diagnosis.
   - No damage is seen in the intestine compared to CD.
   - In many cases, this condition can be controlled by changes in lifestyle including diet and stress management.
5. Refractory Celiac Disease (RCD): In the majority of people with CD, a GFD is sufficient to allow for clinical improvement and improved biopsy results.

• RCD is a severe form of CD that belongs to a subset of NRCD.
• This is a rare condition affecting 1-2% of patients with CD and up to 10% of those with NRCD. Damage to the small intestine continues despite a strict GFD and no evidence of another disease, including cancer (lymphoma).
• RCD can be further subdivided into type I and type II. This distinction is based on a special type of white blood cells seen on the biopsy of the small intestine.
• RCD type I has a better clinical course and survival than RCD type II.

Other diagnoses that may be associated with CD include inflammatory bowel disease and lactose or fructose intolerance (caused by mucosal damage from CD). These conditions should be excluded and treated correctly.

Take Home Messages:

• In the majority of people with CD, a GFD is sufficient to allow for clinical improvement and improved biopsy results.
• A minority of patients will still have symptoms 6-12 months after starting a GFD.
• The most common cause of ongoing symptoms and abnormal lab values is cross contact with gluten.
• GFD adherence should be supported by the guidance of an expert dietitian, advocacy groups, and regular clinic visits.
• Treatment of other causes of NRCD depends on the cause.

Table 1:
# Causes of Nonresponsive Celiac Disease

<table>
<thead>
<tr>
<th>Cause</th>
<th>Typical Features/Tests</th>
<th>How Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gluten exposure (see Chapter 29)</td>
<td>Evaluation by dietitian skilled in celiac disease</td>
<td>Very common</td>
</tr>
<tr>
<td>Irritable bowel syndrome (see Chapter 36)</td>
<td>None</td>
<td>Very common</td>
</tr>
<tr>
<td>Lactose intolerance or fructose malabsorption (see Chapter 37)</td>
<td>Trial of lactose or fructose restriction; lactose or fructose breath testing</td>
<td>Somewhat common</td>
</tr>
<tr>
<td>Microscopic colitis (see Chapter 39)</td>
<td>Biopsy of colon</td>
<td>Somewhat common</td>
</tr>
<tr>
<td>Small intestinal bacterial overgrowth (see Chapter 40)</td>
<td>Breath testing and or a response to antibiotic therapy</td>
<td>Somewhat common</td>
</tr>
<tr>
<td>Refractory celiac disease (see Chapter 43)</td>
<td>Biopsy of small intestine</td>
<td>Rare</td>
</tr>
<tr>
<td>Eating disorder (see Chapter 30)</td>
<td>None</td>
<td>Rare</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Biopsy of small or large intestine; imaging studies of intestine</td>
<td>Rare</td>
</tr>
<tr>
<td>Pancreatic exocrine insufficiency</td>
<td>Stool levels of chymotrypsin or elastase</td>
<td>Rare</td>
</tr>
<tr>
<td>Motility disturbances (too slow or too fast movement of food through the intestine)</td>
<td>Gastric emptying study, intestinal transit testing</td>
<td>Rare</td>
</tr>
<tr>
<td>Food allergy (see Chapter 35)</td>
<td>Allergy testing (skin or blood)</td>
<td>Very rare</td>
</tr>
<tr>
<td>Cancer</td>
<td>Endoscopy, imaging studies of intestine</td>
<td>Very rare</td>
</tr>
</tbody>
</table>

From Shailaja Janna, MD, and Daniel A. Leffler, MD: Nonresponsive Celiac Disease. In Red Life with Celiac Disease: Troubleshooting and Thriving Gluten Free by Melinda Dennis, MS, RD, LDN, and Daniel A. Leffler, MD. www.reallifeceliacdisease.com
Figure 1: An approach to the investigation of Nonresponsive celiac disease

Non responsive CD

Review original diagnosis

Confirmed CD

Dietary review and f/u celiac serologies

Gluten contamination

Education on GFD by expert dietician and monitor progress

No Celiac Disease

Evaluate for other etiologies**

Gluten-free diet

Small bowel biopsies (± Colon biopsies if persistent diarrhea)

Villous Atrophy

Exclude other etiologies of villous atrophy *

Refactory CD

No Villous Atrophy

Consider alternative etiologies for ongoing symptoms**

Supporting evidence

- Confirmation of small bowel histology findings consistent with celiac disease
- Positive TTG, DGP or EMA serology at some time during the clinical course
- Presence of HLA DQ2 or DQ8
- Biopsy proven dermatitis herpetiformis
- Clinical and/or histological response to GFD
- Family history of CD

* Autoimmune enteropathy, combined variable immunodeficiency, collagenous sprue, small intestinal bacterial overgrowth (SIBO), Crohn’s disease, tropical sprue, eosinophilic enteritis, and peptic duodenitis
** Irritable bowel syndrome, SIBO, food intolerances, eosinophilic enteritis, microscopic colitis, and Crohn’s disease

References:


