Level 2

Non Responsive Celiac Disease

KEY POINTS:

- Currently, the only treatment for CD is strict life-long adherence to a gluten free diet (GFD). Nonetheless, a minority of cases will fail to improve or may relapse while on the diet and are classified as non-respondents.

- Non responsive Celiac Disease (NRCD) affects 7-30% of patients on a gluten-free diet.\(^1\) It may be defined as the persistence of manifestations suggestive of CD despite dietary gluten avoidance for 6-12 months.\(^2\)

- NRCD can be further classified as primary or secondary. Primary refers to an initial failure to achieve symptomatic response on a GFD, whereas secondary is a re-emergence of symptoms while on a GFD.\(^1\)

- When the symptoms fail to improve or recur, proper evaluation should be followed to identify and treat the specific cause (See Figure 1).\(^3\) It is important to review and carefully examine the initial diagnosis of CD based on the history of symptoms, signs, laboratory tests, and histological evaluation 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 physician assess intestinal healing and other conditions that can cause similar histological findings (See articles on “Blood Tests” and “Endoscopy” on www.celiacnow.org).

- The most common cause of NRCD is deliberate or unintentional gluten ingestion. Gluten exposure accounts for 35-50% of ongoing symptoms in patients with CD.\(^2\) For this reason, it is extremely important to obtain appropriate dietary advice from an expert celiac dietitian. 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 secondary to CD.

- A positive blood test for CD could be helpful to assess gluten contamination and adherence to GFD but it is important to remember that a normal blood test does not exclude gluten contamination as a possibility.

- After a dietitian’s assessment of dietary causes has been excluded, a small intestinal biopsy should be repeated and compared with the initial biopsy. A
normal or near normal biopsy will lead to consideration of other possible causes (See Table 1).4

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 that creates imbalance in the gut flora resulting in overgrowth of the harmful bacteria.
   - This condition can be easily diagnosed with a hydrogen and methane breath test and treated with a course of antibiotics.
   - The use of prebiotics and probiotics may also be useful. For more information on SIBO, please refer to the SIBO articles under “Nutritional Considerations on the Gluten-Free Diet” or “Non Celiac Enteropathy” on www.celiacnow.org.

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.5
   - The diagnosis is made by colonoscopy and confirmed by histological evaluation under the microscope (thus the name microscopic).
   - Treatment varies depending on the persistence and severity of symptoms. For more information on Microscopic Colitis refer to Chapter 39: Microscopic Colitis and Celiac Disease in Real Life with Celiac Disease.

3. Pancreatic insufficiency:
   - Pancreatic insufficiency is caused by insufficient production of digestive enzymes by the pancreas leading 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 fat in the stool.
   - Treatment is based primarily on pancreatic enzyme replacement therapy but 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, associated with bowel changes that are commonly relieved by bowel movements. Other symptoms such as bloating, diarrhea and/or constipation are required to establish a diagnosis.
   - No permanent damage is seen in the intestine compared to CD.
   - In many cases, this condition can be controlled by lifestyle modifications including diet and stress management.
5. Refractory Celiac Disease (RCD):\textsuperscript{2,6,7}
- 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 about 10\% of NRCD. There is persistence of intestinal damage despite a strict GFD and no evidence of another pathology, including cancer (lymphoma).
- RCD can be further subdivided into type I and type II. This classification 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.

\textbf{TAKE HOME MESSAGES:}
1. In the majority of people with CD, a GFD is sufficient to allow for clinical and histological improvement.
2. A minority of patients will remain symptomatic 6-12 months after starting a GFD.
3. The most common cause of ongoing symptoms and laboratory abnormalities is gluten contamination, either intentional or unintentional.
4. GFD adherence should be supported by the guidance of an expert dietitian, advocacy groups, and regular clinic attendance.
5. Treatment of other causes of NRCD depends on the underlying etiology.
<table>
<thead>
<tr>
<th>Cause</th>
<th>Typical Features/Tests</th>
<th>How Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gluten exposure (see Chapter 20)</td>
<td>Evaluation by dietitian skilled in celiac disease</td>
<td>Very common</td>
</tr>
<tr>
<td>Irritable bowel syndrome (see Chapter 38)</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 Jamma, MD, and Daniel A. Leffler, MD: Nonresponsive Celiac Disease. In Real Life with Celiac Disease: Troubleshooting and Thriving Gluten Free by Melinda Dennis, MS, RD, LDN, and Daniel A. Leffler, MD. www.reallifewithceliacdisease.com
Figure 1: An approach to the investigation of Nonresponsive celiac disease

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
- Presence of associated autoimmune disorders


* 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


