The new ESPGHAN\(^1\) guidelines for the diagnosis of celiac disease

In the last 20 years the perception as well as the diagnosis of celiac disease (CD) have changed. With regard to these developments, the ESPGHAN has released new guidelines for the diagnosis of CD.\(^2\)

Celiac disease (CD): new definition

CD is an immune-mediated systemic disorder elicited by gluten and related prolamins in genetically susceptible individuals and characterized by the presence of a variable combination of gluten dependent clinical manifestations, CD-specific antibodies, HLA-DQ2 or DQ8 haplotypes and enteropathy.\(^2\)

CD testing: two new algorithms

Since CD may present with a large variety of non-specific symptoms, the ESPGHAN recommends testing of two groups: children or adolescents with symptoms or signs suggestive of CD (including atypical symptoms) and asymptomatic children or adolescents with CD associated conditions.\(^2\) (see p. 2)

Intestinal biopsy: no longer the gold standard

In contrast to the old guidelines not only a Marsh 3 but also a Marsh 2 lesion has now been accepted as compatible with CD. The histological features in CD may be patchy and, in a small proportion of CD patients, appear only in the duodenal bulb. The alterations are not specific for CD and they may be found in enteropathies other than CD. This weakens the significance of the biopsy and simultaneously places much more value on serological markers.

Serological tests: sufficient for diagnosis in certain cases

If tTG IgA antibody titers are high and the result is confirmed, CD can now be diagnosed without performing a biopsy. Based on serological first line tests (tTG IgA, total IgA, DGP IgG) two new algorithms for the two groups in which testing is recommended have been developed. A multiple of the upper limit of normal (equivalent to the optimal cut-off) of the tTG IgA test is used as decisive value for how to proceed further. This key part of the algorithms was developed based upon experiences with the Celikey\(^*\) (tTG IgA) kit from Phadia.\(^3\)

What’s new in the guidelines:

- Celiac disease: new definition
- CD testing: two new algorithms
- Intestinal biopsy: no longer the gold standard
- Serological tests: sufficient for diagnosis in certain cases
- CD diagnosis: a revolution in methodology

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New ESPGHAN guidelines – two new algorithms for the diagnosis of celiac disease:

### Algorithm 1: For children or adolescents with symptoms or signs suggestive of CD (including atypical symptoms).*

<table>
<thead>
<tr>
<th>tTG IgA+total IgA or DGP IgG</th>
<th>Refer to gastroenterologist</th>
</tr>
</thead>
<tbody>
<tr>
<td>positive</td>
<td></td>
</tr>
<tr>
<td>negative</td>
<td>Diagnosis: not CD</td>
</tr>
</tbody>
</table>

- **tTG IgA > 10x ULN***
  - EMA + HLA
    - both pos: Biopsy
      - ≥ Marsh 2: Diagnosis: CD
    - EMA neg/HLA pos: Biopsy
      - ≥ Marsh 2: Diagnosis: CD

- **tTG IgA < 10x ULN***
  - EMA + HLA
    - both pos: Biopsy
      - ≥ Marsh 2: Diagnosis: CD
    - EMA neg/HLA pos: Biopsy
      - ≥ Marsh 2: Diagnosis: CD

*Children and adolescents with the otherwise unexplained symptoms and signs of chronic or intermittent diarrhea, failure to thrive, weight loss, stunted growth, delayed puberty, amenorrhea, iron-deficiency anemia, nausea or vomiting, chronic abdominal pain, cramping or distension, chronic constipation, chronic fatigue, recurrent aphthous stomatitis (mouth ulcers), dermatitis herpetiformis-like rash, fracture with inadequate traumas / osteopenia / osteoporosis, abnormal liver biochemistry.

### Algorithm 2: For asymptomatic children or adolescents with CD associated conditions.**

<table>
<thead>
<tr>
<th>HLA (+ optional tTG IgA)</th>
<th>tTG IgA + total IgA or DGP IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>positive</td>
<td>negative</td>
</tr>
<tr>
<td>Diagnose: not CD</td>
<td></td>
</tr>
</tbody>
</table>

- **tTG IgA > 3x ULN***
  - Biopsy
    - ≥ Marsh 2: Diagnosis: CD

- **tTG IgA < 3x ULN***
  - EMA
    - positive: Biopsy
      - ≥ Marsh 2: Diagnosis: CD
    - negative: Diagnosis: not CD

**Asymptomatic children and adolescents with increased risk for CD such as subjects with type 1 diabetes mellitus, Down syndrome, autoimmune thyroid disease, Turner syndrome, Williams syndrome, selective IgA deficiency, autoimmune liver disease, and 1st degree relatives with CD.

*ULN: upper limit of normal; optimal cut-off

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CD diagnosis: a revolution in methodology

The new ESPGHAN guidelines are large step forward in the diagnosis of CD. Their aim is to achieve a high diagnostic accuracy while reducing the burden for the patients and their families. This is achieved through the combination of highly reliable antibody tests (tTG IgA and DGP IgG) and genetic testing which makes the inconvenient and expensive procedure of duodenal biopsy obsolete in many cases.