Reviewer's report

Title: Symptoms and signs in latent celiac disease - a validation study

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Reviewer: Kamran Rostami

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In this study Ludvigsson and his co-worker have identified 3,736 individuals with positive serology and normal biopsy (Marsh 0). From this group they randomly have selected 120 cases for this study and 112 fulfilled the criteria. They suggest using a link between biopsy and serology is an effective model for identifying latent coeliac disease (CD).

This study seems to me very interesting as the atypical presentation in CD (like Microscopic enteritis) is predominant and the attention should be given to the symptomatic patients with atypical serology and histology. I would be supporting them if they would be willing to adjust their manuscript!

Let start with the fact that this study is difficult to read and there are some confusions on the definition of some terminology like latent CD. The treatment approach toward this subgroup of patient is different in this study compared to what was recommended in previous guidelines. The authors do not explain why they use this strategy. I don’t understand; based on what 13% (8-21%) of patients with normal histology have been treated with GFD?

The authors identified 3,736 symptomatic individuals with positive serology and normal biopsy and they consider them as having latent CD. They have selected 120 individuals with 40 +ve for tTGA, 40 +ve for EMA and 40 +ve for AGA for manual reviews of biopsy reports and patients charts review.

As mentioned in discussion, AGA is far less sensitive and specific for CD. Latent CD and the way is described in this study is confusing the clinician. Latent refers specifically to patients who have abnormal antibody blood tests for celiac disease and normal small intestines but no signs or symptoms of celiac disease. Latent CD are not usually the best candidates for Gluten Free Diet for above reason. Therefore I think the title is not representing the findings of this study and should be changed.

Positive serology may occur in other condition too. How the authors are confident that the antibodies are not due to other co-morbidities especially those with positive AGA. The best would be to use the AGA positive group as AGA positive not latent CD! And compare the clinical presentation with tTG and EMA positive group!

Result
This statement is just inappropriate; We identified 3,736 individuals with latent CD!

As mentioned above not every patient with positive serology means latent celiac disease! Please revise; you may say that you identified 3.736 individuals with positive serology and normal biopsy instead!

This is very confusing; In 90% (95% CI=83-95%; 103/114) of individuals undergoing validation, latent CD could be confirmed through patient charts.

Or 46% (36-55%) had diarrhea, while 26% (18-35%) had anemia 90%, 46% and 26% of whom? You perhaps are talking about 114 selected cases. Please clarify for the readers!

Histology

With all respect for the work of Swedish pathologists, Im not conformable with the Swedish house criteria for diagnosing CD. It might be appropriate for internal publication and use but as BMC Gastroenterology has a wider range of readers I would suggest using the classical criteria Rostami et al, Sensitivity of Antiendomysium and Antigliadin antibodies in untreated Celiac Disease: disappointing in clinical practice. Am J Gastroenterol. 1999; 94:888-94 as used in American;


European guidelines;


This would give a more familiar histological picture to the readers!

-There are some confusing numbers used; in abstract 120 latent CD in results 114 in discussion 112 and in table/flowchart 118!!! Please unify!

What does all these % 46% (36-55%), 26% (18-35%) ,, means

Discussion

Discussion is not focussed and the message is unclear and doesn’t appear to come cross the way as it should!

In discussion the authors need to justify why this strategy is effective? why should we look for latent CD?

In contrast to the authors finding Latent CD have no symptoms. However, the reason for biopsy and serology in this study group was based mainly on their symptoms. How do the authors explain this? The authors could bring more life in their discussion by discussing the possibility of microenteropathy and microscopic enteritis as a sole explanation for this fashion of presentation. We
know that relying on villous atrophy would result in missing a significant number of cases. We also know that inflammatory anaemia and inflammatory malabsorption would happen within normal looking mucosa.

Conclusion is not conclusion at all! It is a repeating version of results. Please delete or change!

The authors may emphasise in conclusion that CD may present in a great deal with microscopic enteritis and symptomatic seropositive cases might benefit from a gluten free diet as absence of villous atrophy is not evidence of absence of CD.

**Level of interest:** An article of importance in its field

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

'I declare that I have no competing interests'