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Reviewer's code: 02446483

COMMENTS TO AUTHORS

Non celiac GS can manifest with extraintestinal manifestations and the manuscript is mostly covering these aspects. However, I am missing two aspects in this review, the precise Oxford level of evidence, which does not seem it has been mentioned and the confusing topic of demyelinating neuropathy associated with NCGS. The first is important to address to make your review sounding. The second should be investigated searching if regions of the globe with high density of multiple sclerosis present an increased ratio of NCGS.

In the revised paper, we expressed the level of evidence as you suggested using the Oxford consensus (reference 9). Our search did not retrieve any paper about the association between multiple sclerosis and NCGS, except for the case reports we have already mentioned. Indeed, since the first definition of gluten sensitivity dates back to 2011, papers, which have been published before this date, argued about a too vague relationship between demyelinating diseases and "gluten". For this reason, in Table 3 we reported a low level of evidence (4) for this topic according to Oxford classification.

Manuscript NO: 38672

COMMENTS TO AUTHORS

Losurdo et al. reviewed the literature and wrote Extra-intestinal manifestations of non celiac gluten sensitivity. the proposed that similarly to celiac disease, it shows a systemic involvement, therefore several extra-intestinal manifestations have been hypothesized and investigated in many studies. this is very interesting study. I really enjoyed to read it. I have minor comment: Some parts are explain other GRD like CD and DH and WA. please change the title accordingly.



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Our review was focused only on gluten sensitivity. In some cases we mentioned CD, DH and WA essentially in consideration of some similarities with gluten sensitivity. On these bases, we hypothesized that some extraintestinal manifestations of CD could characterize gluten sensitivity as well. Therefore, we believe that it is not appropriate to change the title, as the topic of the paper is entirely focused on NCGS.

Also add the diagram for the study design, change the table and high and low correlation put in spereat column

We planned our article as a narrative review and not as a systematic review. Nevertheless, in the revised version of the manuscript we enclosed a paragraph reporting search terms and a flow diagram summarizing the process of articles selection (Figure 1). We searched in PubMed database in February 2018 using the following terms: gluten sensitivity, extra-intestinal, autoimmune, thyroid, neurology, psychiatry, rheumatology, skin, dermatology, nutrition, irritable bowel syndrome and fibromyalgia. In this way, 880 articles were found, and, as reported in the flow chart in Figure 1, we selected 86 studies for this review. Other studies which were not focused on NCGS or reporting an unclear definition of NCGS, or in which results about extra-intestinal manifestation were not listed have been excluded. We believe that this figure could help the reader to understand the complexity of the problem and the heterogeneity of the literature on the topic. Finally, we changed the table as suggested also by reviewer 1, enclosing the Oxford level of evidence (reference 9).

Manuscript NO: 38672

COMMENTS TO AUTHORS

This is a concise review of an interesting topic, NCGS. The manuscript is well-written and covers the spectrum of extra-intestinal manifestations and disease associations of NCGS. I have the following comments/suggestions for the Authors:



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1. The key words should include "gluten-related disorders".

As the reviewer suggested, we added "gluten-related disorders" to the key words.

2. The Authors should clarify the difference between disease "association" and disease "manifestations"; actually, table 1 should be divided accordingly.

In the revised version of the manuscript, we modified the table (current table 3) in order to divide extra-intestinal manifestations and associated disorders.

3. A table summarizing studies examining the role of gluten and wheat in IBS should be added.

We added a table (table 2) summarizing the most important studies that examined the role of gluten and wheat in IBS.

4. Another table illustrating prevalence studies of individuals avoiding gluten-based products should be added.

As suggested, we enclosed a table (table 1) reporting the avoidance rate of gluten-containing foods in the revised manuscript.