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RESPONSE LETTER

ESPS manuscript NO: 31200
Manuscript Type: OBSERVATIONAL STUDY
Title: Role of capsule endoscopy in suspected celiac disease: a European multi- centre study

Thank you very much for reviewing our manuscript. We have sent you the following documents and corrections

1) We re-attach the article to all the corrections of the reviewers (31200-Edited.pdf)
2) In this document are added also clarifications that are not included in the article.
3) In response to all reviewers about the language: we attached the document certifying that the manuscript listed below was edited for proper English language, grammar, punctuation, spelling, and overall style by one or more of the highly qualified native English speaking editors at Wiley Editing Services.

CLARIFICATIONS TO THE REVIEWER'S COMMENT- Reviewer's code: 02462725

1) FIRST QUESTION

1.1.Inclusion criteria: An analysis of the clinical histories of 163 patients (mean age = 46.4±17.3 years, range: 11-85; 68.1% women) was conducted; the patients underwent CE for suspected CD during the years 2003-2015. The suspicion of CD was based on a clinical assessment indicating symptoms that were compatible with CD, serology (ATG and to rule IgA deficit) and histology. In selected cases HLA status DQ2 / DQ8 (in doubtful cases). Family history of CD were collected. All patients underwent gastroscopy to determine the basal histology except when endoscopy was contraindicated. Depending on the protocol for each centre, there were 2-6 DB (of the bulb and/or second duodenal portion). Intestinal damage was calculated using the Marsh classification [17], with stages III and higher considered positive.
1.2. Exclusion criteria: Patients with a strong CD diagnosis (positive histology and serology) were excluded (n=189), as were those who underwent CE due to suspicion of another non-celiac pathology, or requests for obscure gastrointestinal bleeding without other data suspicion of CD.
1.3. Diagram 1: Groups with suspected CD included and excluded in the study

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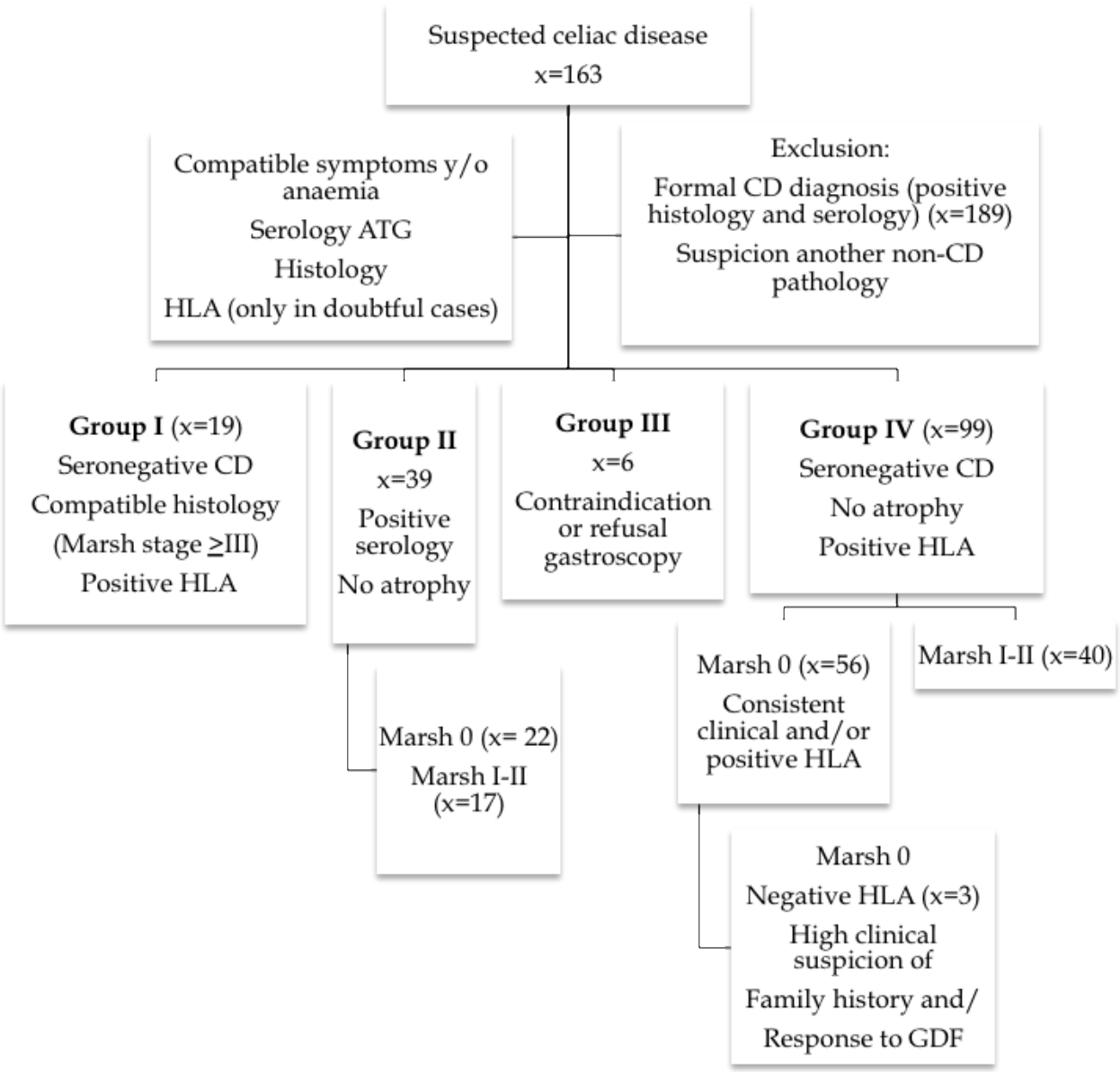

2) SECOND QUESTION

A study of the incidence of CD by / without EC was not the objective of our work and since it is retrospective multicentric and covers a large period of time it would not be reliable nor would have internal validity to calculate it. Our study analyzes the impact of the EC on the suspicion of CD, so we do not know the number of excluded cases with a definitive diagnosis of previous CD, which would not contribute information relevant to the EC value in the suspicion of CD, since this Is done in cases of doubt and not those with firm diagnosis through other tests.

We are NOT estimating the impact and usefulness of the CE in celiac disease in general, for which we would need the total number of cases with suspected CD and with confirmed CD, we are estimating the usefulness of the CE in very specific cases of CD. We suspect dubious CD as defined in our methodology, therefore we only need these selected cases, and not the entire CD population. Therefore, the applicability of our study is not for the global CD, but for the doubtful cases that are described in groups I-IV.

3) THIRD QUESTION

Clarification is included on page 14 of the manuscript:
As for the finding of ulcers in the UJ, they are distinguished from those found in other enteropathies or in patients without pathology because they are more numerous (> 5) and larger and distal [32]. Likewise, the distinction with other ulcerative diseases should be made in a context of adequate suspicion and after response to specific treatment.

CLARIFICATIONS TO THE REVIEWER'S COMMENT- Reviewer's code: 03647086

1. *According to the authors' objective, I believe that the most important matter is the percentage which the diagnosis was changed from the suspicious to the definitive CD. Please provide it in this manuscript.*

Since this is a retrospective study, we have not collected the overall final diagnoses of CD, but only the diagnostic impacts of the technique. We do not have a percentage of patients with definitive global CA as we have not measured it directly or have established it in the methodology. We have measured the diagnostic impact of EC and its therapeutic impact, which are data that can be approximated to definitive CD diagnoses. It is impossible to know because to analyze the true diagnoses of CD we would have to know how many were diagnosed at the end of CD independently of the EC. For example: there may be a positive and non-atrophic Ac case that the EC is normal but in the future has atrophy in a gastroscopy and is diagnosed as having celiac disease.

2. *If authors have data how many cases could be shown the histological atrophy with the biopsy using deep enteroscopy that depend on the result of SBCE in without atrophy groups, please provide it.* .

We know the number of enteroscopies but in our database it is not determined if the biopsy was taken by enteroscopy or by gastroscopy because many patients have both examinations done after the EC. Thus, we cannot calculate it.

3. *The mean age and every frequency are up to one decimal place. It was slightly busy.*

We have simplified all data with a single decimal throughout the manuscript

CLARIFICATIONS TO THE REVIEWER'S COMMENT- Reviewer's code: 03029658

1. GENERAL COMMENTS

- Abbreviations: negative predictive value - NPV; Standard deviation - SD, have been deleted
- The abbreviation for ulcerative jejunitis (UY) has been changed to UJ

2- SPECIFIC COMMENTS

- The age factor is corrected in the sections: summary and results:
  - page 4: Factors associated with a greater DY were positive serology (68.3% vs. 49.2%, p=0.034) and older age (p=0.008).
  - page 10: Positive serology (68.3% vs. 49.2%, p=0.034) and older age (50±17 vs. 43±17, p=0.008) were associated with a larger impact on diagnosis

- Introduction: We change the phrase about genetic factors

The diagnosis of CD requires the analysis of clinical, histopathological, and serological factors. Genetic factors are not performed routinely, they only help in dubious cases. These has a role primarily exclusion of this diagnosis by its high negative predictive value

- Methods: inclusion of a flowchart with the 4 groups of patients 1

See Diagram 1: Groups with suspected CD included and excluded in the study

- Results: We have simplified all data with a single decimal throughout the manuscript

- Strengths of the study:

We have removed the strengths paragraph and have included it in the Comments section

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CLARIFICATIONS TO THE REVIEWER'S COMMENT- Reviewer's code: 03478442

1) FIRST QUESTION

Within group four (*n*=99) was included patients seronegative and Marsh stages 0 (*n*=59). Patients showed consistent clinical and/or anaemia and positive HLA. We only included 3 patients Marsh 0 and negative HLA because the authors considered that they had factors of high suspicion: high clinical suspicion, other family members and/or to advise those who need for accurate diagnosis for response to GFD and need to maintain or withdraw it. We excluded those who were HLA negative when the only suspect data point was clinical presentation.

2) SECOND QUESTION

The interpretation of results is not varied in relation to the type of capsule given that each center has experience with one of them

3) THIRD QUESTION

NCGS (*n*=15/39, 38.46%), was diagnosed in symptomatic patients of Group-IV (seronegative CD without atrophy) exclusively when they clinically responded to the GFD started after normal CE results without any further confirmation of classic CD.