November 25, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13950-Edited CD3 article Final.doc).

Title: **Immunohistochemical CD3 staining detects additional patients with celiac disease**

A prospective study

Author: A Mubarak; VM Wolters; RHJ Houwen; FJW ten Kate

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 13950

The manuscript has been improved according to the suggestions of reviewers:

1. The format has been updated.

2. Revision has been made according to the suggestions of the reviewer

1. The definition of the ESPGHAN criteria is now added in the first part of the discussion section:

   'Even after recent update of the ESPGHAN guidelines for the diagnosis of celiac disease, which state that a biopsy can be omitted in symptomatic cases with very high tTGA levels, positive EMA and the disease related human leukocyte antigen types, for most patients histological assessment of duodenal biopsies is still necessary for the diagnosis.'

2. The gold standard for the diagnosis of celiac disease and how it was stated that the CD3 diagnosis was correct, were unclear according to the reviewer.

   The study included children with a suspicion of celiac disease and all patients carried the disease associated HLA type. So, based on clinical grounds those children could have celiac disease. In case of discrepant diagnosis between the HE and CD3 section the final diagnosis was based on the the serological data of the patients. This is now emphasized in the Methods section:

   'In case of discrepancy between the HE and CD3 section, the final diagnosis was based on the serological data of the patients. For example, a patient with positive serology who has crypt hyperplasia and villous atrophy, but increased IEls only on the CD3 sections (so on the HE sections no diagnosis of celiac disease but on the CD3 sections a Marsh III lesion), was considered to have celiac disease. Similarly, in patients with negative serology and a Marsh 0 on the HE section but a Marsh 1 on the CD3 sections, the final diagnosis was considered to be a Marsh 0.'

3. The abbreviations of tTGA and EMA are now explained:
   'Results of anti-endomysium antibodies (EMA) and anti-tissue transglutaminase antibodies (tTGA) as well as the clinical data of the patients were collected from the medical records.'

4. Histological figures are now added.

3. References and typesetting were corrected

4. With regards to the files related to the academic rules and norms:

   -This study was performed according to the rules of the local medical ethical committee. Because all researches were also doctors involved in all cases and because no additional tests than the routine tests were performed, the medical ethical committee does not require additional approval or acquisition of informed consent. In fact, only the doctors who were treating the patients could see the data. In addition, no additional biopsies were taken and HE and CD3 staining are performed routinely in our hospital, so no additional intervention was done. In conclusion, this study is an observational study without any intervention and only doctors involved in the cases could see the data, which does not require obtaining additional approval or informed consent. In addition, the dataset and analysis were anonymized. Therefore, we do not have any documents (approval by medical ethical board) to submit.

   -The statistical analysis of this study was simple and did not require the involvement of a statistical expert. So we do not have a report by a biostatistician.

Thank you again for publishing our manuscript in the World Journal of Gastroenterology.

Sincerely yours,

Dr. Amani Mubarak