Format for ANSWERING REVIEWERS

August 25, 2012

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 12902-revised.doc).

Title: Clinical and diagnostic aspects of gluten related disorders

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Name of Journal: *World Journal of Clinical Cases*

ESPS Manuscript NO: 12902

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

1 Revision has been made according to the suggestions of the reviewer

Referee 28366

1. This is very interesting paper and it is written well. however it is similar to other papers published so far. I would like the authors explain, what this paper will add to the current existent literature?

Our review aims to provide readers with the latest updates regarding gluten-related disorders, in particular ESPGHAN guidelines for the diagnosis of celiac disease and state of the art concerning NCGS (with particular attention to Second Consensus Conference document.
We added a sentence in the Core Tip explaining this concepts: *"In particular, this paper will cover the most important news from ESPGHAN guidelines for celiac disease and the state of the art of the research about non-celiac gluten sensitivity"*

2. I suggest to discuss biomarkers or immunogenetic only using the reference below Amado Salvador Pena. Immunogenetics of non celiac gluten sensitivity, Gastroenterol Hepatol Bed Bench 2014;7(1):1-5

We suppose the Reviewer referred to the immunogenetic of NCGS. Discussion and proper reference were added to Non-celiac gluten sensitivity session.

Referee 68090

1) Patients with non-coeliac gluten sensitivity (NCGS) can experience a range of gastrointestinal

and extraintestinal symptoms. The authors must include that NCGS-associated depression might share similar pathophysiological mechanisms to other neurological manifestations observed in gluten-related disorders, such as ataxia and encephalopathy. Several studies suggested a relationship between NCGS and neuropsychiatric disorders, particularly autism and schizophrenia

Both of these aspects have been added to the NCGS section
"Interestingly, mood disorders in NCGS may recognize similar pathophysiological mechanisms to other neurological manifestations observed in gluten-related disorders such as GA, as accumulated toxic insults often resulting from adverse chemical exposures might lead to hypersensitivity and impaired tolerance of the immune system (i.e. the so-called "toxicant induced loss of tolerance")
Several studies suggested a relationship between NCGS and neuropsychiatric disorders, particularly autism and schizophrenia, however the role of NCGS in conditions affecting the nervous system remains a highly debated and controversial topic that requires additional, well-designed studies to establish the real role of gluten as a triggering factor in these diseases".

2) It has been suggested that wheat proteins other than gluten, such as amylase trypsin inhibitors, can contribute to non-coeliac gluten sensitivity disorder. In addition, recent studies have emphasized the possible role of fermentable oligosaccharides, monosaccharides and disaccharides and polyols (FODMAPs) in the development of this syndrome. Interestingly, together with milk, legumes, honey, some fruits (watermelon, cherry, mango, pear) and some vegetables (chicory, fennel, beetroot, and leek), the most common food sources of FODMAPs also include wheat and rye, the same grains and cereals that also contain gluten proteins. Lack of biomarkers is still a major limitation of clinical studies, making it difficult to differentiate NCGS from other gluten related disorders Moreover, the use of a wide array of symptom evaluations and lack of a standardized symptom scoring form represent major obstacles to further progress. The authors must include these aspects

The role of FODMAPS and the lack of biomarkers had already been stressed in the NCGS section of our paper

3) The clinical entity NCGS resembles, and may well be a part of, irritable bowel syndrome. The diagnosis of both conditions is based on clinical work-up; objective biomarkers are not available and may be difficult to develop. NCGS may be caused by improper immune responses, intolerance to poorly digestible and fermentable substances in the wheat, or a combination of these. The observation that some patients respond with symptoms after ingestion of grains in the absence of CD or wheat allergy cannot be ignored. Symptoms are characterized by both gastrointestinal and extraintestinal symptoms that are reminiscent of those that occur in individuals with IBS. Whether it is the gluten or the grain that is responsible for these symptoms remains to be defined better for the authors.

Characteristic symptoms of NCGS had been reported "From a clinical point of view, NCGS patients may display a great variability in gastrointestinal (bloating, abdominal pain, diarrhea, nausea, aerophagia, aphtous stomatitis, constipation) and extraintestinal symptoms (lack of well being, tiredness, headache, anxiety, foggy mind, numbness, joint or muscle pain, skin rash, anemia,

dermatitis)"
As already said in the latest point, the role of FODMAPs and ATI had also been widely discussed.

4) More or less 35% with celiac disease developed ataxia and peripheral neuropathy. The incidence of neurological manifestations related to celiac disease has been estimated to be 6-10%. Other neurological manifestations are epilepsy, cognitive disorders, dementia, tremor, myelopathy, neuropathy, brainstem encephalitis, progressive leukoencephalopathy, vasculitis, occipital calcification, anxiety/depression, and myoclonic syndrome. They also include neuromuscular manifestation such as peripheral polyneuropathy, mononeuropathy multiplex, dermatomyositis, polymyositis, and inclusion body myositis. The authors must include these neurological manifestations of celiac disease

We included epilepsy and peripheral neuropathy as possible manifestation of CD. Extraintestinal symptoms reflect the systemic nature of the disease and include chronic fatigue, anemia, reduced bone mineral density, aphthous stomatitis, high aminotransferase levels, joint/muscle pain and spontaneous abortions, epilepsy, peripheral neuropathy
We consider other conditions as possible associated autoimmune diseases (dermatomyositis/polymyositis, inclusion body myositis, vasculitis) rather than neurological manifestation of CD in a strict sense.

Referees 28840 and 227406

The manuscript has been proofread and edited in order to correct English language errors.

2 References and typesetting were updated

Thank you again for considering our manuscript for publication in the *World Journal of Clinical Cases*.
Sincerely yours,

Francesco Tovoli, MD