November 20, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5540-revised-manuscript.doc) with all the changes are shown by track changes, and the new references are highlighted with yellow.

Title: Epidemiological and clinical characteristics of inflammatory bowel diseases in Cairo, Egypt

Authors : Serag Esmat, Mohamed Elnady, Mohamed Elfekki, Yehia Elsherif , and   Mazen Naga

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5540

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

2 Revision has been made according to the suggestions of the reviewers (Answers to each point of reviewers comments are underlined)
Reviewer 1
The epidemiological and clinical characteristics of inflammatory bowel diseases in Cairo, Egypt
Comments to Authors
This is a cohort study regarding patients diagnosed with IBD in a tertiary hospital of Cairo. Very few data are available in the literature regarding IBD in North Africa. Having epidemiological and clinical information from countries with different life habits, pathogens and parasitic infections is of great interest for allowing a better understanding of the pathogenesis of the disease
Major concerns
1- The male to female ratio is reported differently in the table 2 (16/6) and in the text (1:1,26). The discussion has to be adapted to the real gender data. ?
There was a mistyping; the correct male/ female ratio regarding CD in this study is (1: 2.6). I corrected this mistyping in the results and discussion sections.
The discussion was adapted to the real gender data.

2- In the table 3 the extra intestinal manifestations should be defined ?
The extra intestinal manifestations was defined as recommended in table 3
They are: NO/fatty liver/arthralgia/arthralgia & uveitis – 14/ 1/7/3/3

3- In the tables the localization of CD and extension of UC should be described (UC is described in table 4 but the data should be added to table 2 also) ?
As recommended:
The localization of CD was added to table 3
The extension of UC was added also to table 2

4- The data regarding parasitic infections is of interest but is poorly described and discussed. Is these parasitic infection history similar to that of patients without IBD in the same hospital? Are different parasites involved? When the parasitic infection occurred?
The parasitic infection history in patients without IBD was different and yes different parasites were

involved, in our study the parasites identified among the IBD patients (157) were: Entameba histolotica (19.1 %), Giardiasis (3.2%) and Schistosomiasis (3.2%) while in the patients without IBD (23998) the parasites identified were : Entameba histolotica (20.1 %), Enterobius vermicularis (8.3%) Giardiasis (7.2%), Schistosomiasis (5.4%), Ascaris lumbricoides (2.1%), Ancylostoma duodenale (2.1%), Trichuris trichiura (1.1%), Hymenolepis nana (1%) and mixed infection in 3%.
But unfortunately no more detailed data were available about the parasitic infections including the time of exposure, the number of times of exposure, type of treatment received, complications etc…

5- It has been postulated in the "hygiene hypothesis" that the lack of exposure to helminth infections, as a result of improved living standards and medical conditions, may have contributed to the increased incidence of IBD in the developed world. Epidemiological, experimental, and clinical data sustain the idea that helminths could provide protection against IBD. Is there any data in the hospital indicating the incidence of parasitic infection in a control population?

As mentioned in the previous point in the patients without IBD (23998) the parasites identified were: Entameba histolotica (20.1 %), Enterobius vermicularis (8.3%) Giardiasis (7.2%), Bilharziasis (5.4%), Ascaris lumbricoides (2.1%), Ancylostoma duodenale (2.1%), Trichuris trichiura (1.1%), Hymenolepis nana (1%) and mixed infection in 3%.
These data support the hygiene hypothesis where the exposure to helminthes in patients without IBD was much higher than those with IBD.

6- The paper by N Ruyssers Worms and the Treatment of Inflammatory Bowel Disease: Are Molecules the Answer? Clin Dev Immunol. 2008 can be useful for the discussion?

A new paragraph including discussion about parasitic infections, hygiene hypothesis was added to the discussion section including data from the paper of N Ruyssers Clin Dev Immunol. 2008 as recommended.

7- In the discussion at page 10 the authors state: "The mean age of diagnosis for UC patients residing in Cairo was 27.9 while for those living outside was 25.9 with no statistical significance to denote that IBD is more common among urban than rural populations in Egypt". I believe that the mean age and the statistical analysis done does not allow to draw any conclusion regarding the incidence of the disease in rural vs urban area ?

Yes you are absolutely right because the patients included in this study can't be accurately considered to be representative of the general population
The expression of this information was corrected in the discussion section as follow:

"The mean age of diagnosis for UC patients residing in Cairo was 27.9 while for those living outside was 25.9 with no statistical significance between those living among rural and urban populations. However these findings cannot allow us to conclude differences in the incidence of the disease among urban and rural populations in Egypt".

8- Again the increase in number of patients with IBD in the last years may only represent a stronger role for this hospital in attracting patients from the city and the country having no epidemiological meaning. The authors can consider the increase as an epidemiologic phenomenon but should be cautious in the interpretation considering alternative hypothesis. ?

This information was modified in its expression in the discussion part as recommended.

9- Table 4 shows the changes in activity score over time. This is also an interesting point. Is it the behavior milder than in western countries? This can be another point of discussion.

Yes the behavior seems milder than in western countries and a the total colectomy rate after 5 to 15

years in our study was much lower than the total colectomy rate after 10 years in studies from Western countries ; a discussion of this point was added to the discussion section as recommended.

10- **Minor concerns**
    a-   In the table 2 the numbers of extraintestinal manifestations should be checked ?
The numbers of: Other extra intestinal manifestations in table 2 were checked and corrected.

    b-   Everywhere in the text there are spelling errors and overall the language should be revised.

A complete English revision and editing was done by the American journals experts and a certificate of English edition was sent to the WJG editor [certifies that the manuscript 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 American Journal Experts].

Reviewer 2
1- The manuscript by Esmat and co-authors presents a descriptive study about the characteristics of 157 inflammatory bowel disease (IBD) patients from one single hospital in Cairo, diagnosed from 1995-2009. As the authors claim, there is not much information about the prevalence and characteristics of IBD patients in the Middle East and Northern Africa, which might justify the need for this kind of descriptive reports. Nevertheless, the small number and the heterogeneity of this group of patients can hardly be considered to be representative for this region.
Although the relatively small number and the heterogeneity of our group of patients may not be represented for the general population in Egypt but it Shed light on the striking increased frequency of diagnosis of IBD in the last 10 years of the 15 years duration from 1995 to 2009 . An observation that may predict a future rise in IBD incidence in Egypt reflecting the importance of the need of database and registry documentation of IBD patients and their characteristics to be able to produce more accurate information about the natural history of IBD in Egypt.

2-   A similar report has been issued recently for a cohort of patients from Tunisia with more or less the same approach and conclusions. The actual value of these reports is limited, because there are no comparisons possible, which should culminates in a brief and concise discussion.
A brief discussion to the results of the recent study from Tunisia compared to our results was added and the study was cited in the references.
"Ouakaa-Kchaou A, Gargouri D, Bibani N, Elloumi H, Kochlef A, Kharrat J. Epidemiological evolution of epidemiology of the inflammatory bowel diseases in a hospital of Tunis. Tunis Med. 2013 Jan;91(1):70-3."

3-   Overall the presentation of this paper seems too extensive for the message, with several repetitions (e.g. . 2x protocol is approved by…, 3x Cairo University is a tertiary care referral center, 2x chi-square used for statistical analysis etc.).
All the unnecessary repetitions was removed

4-   Figures 1 to 3 are not necessary.
I removed figures 1 and 2 but I believe that figure 3 is important because it demonstrates one of the most important finding in this study (the striking increase of diagnosis of IBD last 10 years of the 15 years duration from 1995 to 2009) so it can easy deliver this important message to the reader by a fast look without reading the text.

5-   The paper should be more compact or alternatively the data should be integrated in a more review/meta-analysis like paper in which they are compared with the 'global prevalence' as is more or less, but not effective indicated in the discussion.

The Depth of discussion was increased and more comparisons with global natural history and prognosis of IBD were added to the discussion section.

6- The references are not up-to-date. Especially in 2013 a number of relevant papers have been published comparing different ethnical groups.

A complete update to the whole references of the paper was done and many relevant updated references in 2010-2013 were added after citing their valuable information to this paper.

7- Minor points:

a- Abbreviations UC/CD: once introduced, use them.

The abbreviations UC/CD was used all through the paper after their introduction.

b- Patients were included over the last 15 years (= 1994-2009?)

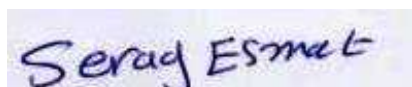This was corrected to "over 15 year's duration from 1995 to 2009."

c- Check specific words like endoscopic etc.

A complete English revision and editing was done by the American journals experts and a certificate of English edition was sent to the WJG editor [certifies that the manuscript 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 American Journal Experts].

3 References and typesetting were corrected

Thank you again for considering our manuscript for publication in the *World Journal of Gastroenterology*.

Sincerely yours,

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