PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association of Parkinson's disease and treatment with aminosalicylates in inflammatory bowel disease: a cross-sectional study in a Spain drug dispensation records.
AUTHORS	Pinel Ríos, Javier; Madrid Navarro, Carlos; Pérez Navarro, María; Cabello Tapia, María; Piña Vera, María; Campos Arillo, Víctor; Gómez García, María; Mínguez Castellanos, Adolfo; Escamilla Sevilla, Francisco

VERSION 1 - REVIEW

REVIEWER	Francisco Portela Centro Hospitalar Universitário Coimbra
REVIEW RETURNED	09-Oct-2018

GENERAL COMMENTS	Authors address a issue that needs more data, namely the relation between IBD and Parkinson's disease. Although the limitations of their study doesn't allow definitively conclusions they add some interesting data namely a possible influence of salicilates.

REVIEWER	Jean-Frederic Colombel Icahn School of Medicine at Mount Sinai
REVIEW RETURNED	13-Oct-2018

GENERAL COMMENTS	There is currently great interest in looking at association between Parkinson and Crohn's disease given recent discoveries of common susceptibility gene (LRKK2). Based on a claims data from Spain the authors here report a possible protective role of aminosalicylates or IBD against PD development. This paper suffers from major weaknesses which make the results difficult to interpret: - The hypothesis is not clear since an association has been found with PD and Crohn's disease (CD) and not ulcerative colitis and 5-ASA are not recommended in the treatment of CD. - There is no experimental rationale to possibly explain how 5-ASA could protect against PD (while there is a strong case for anti-TNFalpha therapy). - The diagnosis of PD or IBD is based on the "proxy" of having received an anti-Parkinson agent or 5-ASA which is not acceptable.

	- The lack of clinical and further granular data associated with this claims report is a major weakness since the diagnosis of PD is based on disputable criteria, nothing is none about temporal relationship between exposure to 5-ASA and occurrence of PD and there is no adjustment for type of IBD, disease activity and possible use of other drugs and notably biologics.

REVIEWER	Ubaldo Bonuccelli University of Pisa-Dept:of Clinical&Experimental Medicine-Neurology Unit Italy
REVIEW RETURNED	14-Oct-2018

GENERAL COMMENTS	This is an interesting study trying to evaluate the relationship between Inflammatory Bowel Disease (IBD) and Parkinson's Disease (PD) by using administrative flow drug data in a large population of about 2 millions of individuals.By the end the coparions were made between about 20.000 possible PD patients and about 7.500 IBD patients:56 patients presented with both diseases associated.PD showed a lower prevalence among IBD patients and this result was reinforced when considering individuals aged less than 65 year s. A few points for the AA: 1.The mean age of IBD patients is quite lower compared to mean age of pD patients and this should be discussed. 2.In the discussion section AA adfirm that the prevalence of PD is 5-fold higher in the study population (2 millions?) but this estimate seems to me not correct (for instance in a similar epidemiological study we have found in the population of Tuscany Region (3.400.000) a number of PD patients of about 18.000 (Reliability of administrative data for the identification of Parkinson's disease cohorts.Baldacci F et al. 2015) suggesting that the prevalence of PD in the present study may be overestimates the real number of PD patients of about 2 folds but not 5 folds. 3.The discussion appears to me too long and I suggest to shorten it leaving aside experimental models of PD and pointing more directly to the strenghts and weakenesses of the study.In particular I recommend to discuss why the lower risk of PD was observed more clearly in the subgroup of individuals aged less than 65.Is it this result determined by a different prevalence of PD and IBD related to the different ages?

REVIEWER	Michael Sachs Karolinska Instutute, Sweden
REVIEW RETURNED	26-Dec-2018

GENERAL COMMENTS	Overall this is a good study that has a balanced discussion and introduction. I have a major issue with the description of the methods and results that I think should be clarified before publication: - The authors describe the study as the formations of three groups: possible PD (and not IBD), possible IBD (and not PD), and possible PD and IBD. This ignores the most important group which is the control group that has neither possible PD nor possible IBD. The analysis description makes it sound like the analysis was restricted only to subjects fitting into one of these three groups

	(lines 10 of page 8), but that is obviously not the case otherwise you wouldn't have been able to estimate the odds ratio. I suggest instead describing the entire study population as the 2020868 subjects that meet the inclusion criteria, and say something like "four groups were defined by the cross-tabulation of the two dichotomous variables of interest, possible PD and possible IBD. Logistic regression was used to estimate the age-sex adjusted odds ratio for the association between IBD and PD." Other minor points: - Page 8, line 42: "The OR for an individual with “Possible PD” being in the “Possible IBD” group was ...". This is not a correct interpretation of the odds ratio. - The article summary states that matching by age and sex was performed, but abstract and article states that regression adjustment was done instead. - What was the rationale for choosing the 65 age cutoff for stratification? Was this chosen a priori, or based on some observation in the data? Was age adjusted for linearly within these strata?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Francisco Portela

We agree with the reviewer, like cross sectional study, the scientific evidence is weak when we intend to establish a causality and we do so in the discussion, because our results only serve to generate hypotheses, which can only be demonstrated with longitudinal and experimental studies in animal models. On the other hand, the sample size is important and this question brings us closer to causality than to chance. We thank you for your time and comments.

Reviewer: 2

Reviewer Name: Jean-Frederic Colombel

- The hypothesis is not clear since an association has been found with PD and Crohn's disease (CD) and not ulcerative colitis and 5-ASA are not recommended in the treatment of CD.

Our hypothesis suggests a lower risk of PD in individuals with IBD (both Crohn's disease and ulcerative colitis) aged ≤65 years and treated with 5-ASA, which may be related to a pharmacological effect on alpha-synuclein aggregation and propagation that could reduce or delay PD onset in at-risk populations.

5-ASA drugs are the first-line treatment in ulcerous colitis, however the use of 5-ASA for Crohn's disease is controversial, but for patients with limited ileitis and mild symptoms, a slow release, oral 5-

ASA agent is suitable such as mesalamine [1,2]. And although some data suggests that 5-ASA is inferior to budesonide for inducing remission, the reality is that most patients with CD, basically with mild CD are treated with 5-ASA.

1. Ford AC, Kane SV, Khan KJ, et al. Efficacy of 5-aminosalicylates in Crohn's disease: systematic review and meta-analysis. Am J Gastroenterol 2011 Apr;106(4):617-29.

2. Lim WC, Wang Y, MacDonald JK, et al. Aminosalicylates for induction of remission or response in Crohn's disease. Cochrane Database Syst Rev 2016 Jul 3;7:CD008870.

- There is no experimental rationale to possibly explain how 5-ASA could protect against PD (while there is a strong case for anti-TNFalpha therapy).

We agree with the evaluation of the reviewer, this experimental rationales is not proven, we suggest that local action mechanisms of 5-ASA, which is not fully elucidated but is considered to include: a) anti-inflammatory activity or inhibition of the local synthesis of prostaglandins and leukotrienes; b) reduction in nitric oxide and IL-6 production and an antiapoptotic effect, diminishing phosphorylation by mitogen-activated protein kinases (MAPKs), e.g., p38 and JNK (c-Jun N-terminal kinases); and c) action on the microbiota, producing qualitative and quantitative changes in its composition; may affect progression of the synucleinopathy, given that they may act on etiopathogenetic mechanisms that would activate microglia, associated with certain microbiota and bacterial membrane lipopolysaccharides or endogenous factors (e.g., JNK and p38) [1]. Alteration of these signaling pathways in PD [2] produces aberrant phosphorylation [3], leading to their proposal as possible therapeutic targets [4,5].

1. Zhang W, Gao JH, Yan ZF, et al. Minimally toxic dose of lipopolysaccharide and α-synuclein oligomer elicit synergistic dopaminergic neurodegeneration: role and mechanism of microglial NOX2 activation. Mol Neurobiol. 2016 Dec 15. [Epub ahead of print].

2. Kim EK, Choi EJ. Compromised MAPK signaling in human diseases: an update. Arch Toxicol 2015; 89(6):867-82.

3. Wang S, Zhang C, Sheng X, Zhang X, Wang B, Zhang G. Peripheral expression of MAPK pathways in Alzheimer's and Parkinson's diseases. J Clin Neurosci 2014; 21(5): 810-4.

4. Moussaud S, Malany S, Mehta A, Vasile S, Smith LH, McLean PJ. Targeting α-synuclein oligomers by protein-fragment complementation for drug discovery in synucleinopathies. Expert Opin Ther Targets 2015; 19(5): 589-603.

5. Wilms H, Rosenstiel P, Romero-Ramos M, et al. Suppression of MAP kinases inhibits microglial activation and attenuates neuronal cell death induced by alpha-synuclein protofibrils. Int J Immunopathol Pharmacol 2009; 22(4):897-909.

- The diagnosis of PD or IBD is based on the "proxy" of having received an anti-Parkinson agent or 5-ASA which is not acceptable.

We agree with this assessment , as we detailed in our paper, it is the main limitation recognized in the discussion (paragraph 9) of the work to have used proxy variables.

- The lack of clinical and further granular data associated with this claims report is a major weakness since the diagnosis of PD is based on disputable criteria, nothing is none about temporal relationship between exposure to 5-ASA and occurrence of PD and there is no adjustment for type of IBD, disease activity ºand possible use of other drugs and notably biologics.

This study has the limitations of cutting studies and the derivative of using proxy variables, with the strength of the selected sample size. We recognize that the evidence is weak but sufficient to carry out longitudinal/experimental studies in this line.

Reviewer: 3

Reviewer Name: Ubaldo Bonuccelli

1.The mean age of IBD patients is quite lower compared to mean age of PD patients and this should be discussed.

We agree with the reviewer, however in the analysis of the data, the relevant age adjustment was made (in the results section, line 20-22).

The inflammatory bowel disease has a bimodal distribution occurring mainly between 15 and 25 years of age, and between 55 and 65 years of age. Classically, inflammatory bowel disease has been considered as a condition that begins in young people, with a peak incidence between the second and fourth decades of life. Some studies have suggested the existence of a bimodal distribution, with a second peak of lower incidence between 60 and 80 years of age. However, inflammatory bowel disease can occur in any age group, both in children and in the elderly. Between 5 and 15% of patients are diagnosed after 60 years of age. We contribute bibliography in relation to epidemiology of inflammatory bowel disease [1,2,3]. We thank you for your time and comments.

1. Rodríguez-D'Jesus A, Casellas F, Malagelada JR. Epidemiology of inflammatory bowel disease in the elderly. Gastroenterol Hepatol. 2008;31(5):269-73.

2. Herrinton LJ, Liu L, Lewis JD, Griffin PM, Allison J. Incidence and prevalence of inflammatory bowel disease in a Northern California managed care organization, 1996-2002. Am J Gastroenterol 2008 Aug;103(8):1998-2006.

3. Takahashi H, Matsui T, Hisabe T, et al. Second peak in the distribution of age at onset of ulcerative colitis in relation to smoking cessation. J Gastroenterol Hepatol 2014 Aug;29(8):1603-8.

2.In the discussion section AA adfirm that the prevalence of PD is 5-fold higher in the study population (2 millions?) but this estimate seems to me not correct (for instance in a similar epidemiological study

we have found in the population of Tuscany Region (3.400.000) a number of PD patients of about 18.000 (Reliability of administrative data for the identification of Parkinson's disease cohorts.Baldacci F et al. 2015) suggesting that the prevalence of PD in the present study may be overestimates the real number of PD patients of about 2 folds but not 5 folds.

We agree with the evaluation of the reviewer, this study has limitations related to the utilization of a drug dispensation record, subjects therefore not be considered representative of the general population. We have clarified this question in the manuscript (section discussion - last paragraph). We thank you for your time and comments.

3.The discussion appears to me too long and I suggest to shorten it leaving aside experimental models of PD and pointing more directly to the strenghts and weakenesses of the study.In particular I recommend to discuss why the lower risk of PD was observed more clearly in the subgroup of individuals aged less than 65.Is it this result determined by a different prevalence of PD and IBD related to the different ages?

We have modified the Discussion section, regarding this comment, in this cross sectional study an adjustment was made in the regression model, so our result is independent of age and sex.

Reviewer: 4

Reviewer Name: Michael Sachs

- The authors describe the study as the formations of three groups: possible PD (and not IBD), possible IBD (and not PD), and possible PD and IBD. This ignores the most important group which is the control group that has neither possible PD nor possible IBD. The analysis description makes it sound like the analysis was restricted only to subjects fitting into one of these three groups (lines 10 of page 8), but that is obviously not the case otherwise you wouldn't have been able to estimate the odds ratio.

I suggest instead describing the entire study population as the 2020868 subjects that meet the inclusion criteria, and say something like "four groups were defined by the cross-tabulation of the two dichotomous variables of interest, possible PD and possible IBD. Logistic regression was used to estimate the age-sex adjusted odds ratio for the association between IBD and PD."

We agree, we have modified it in the manuscript. We analyzed the data with the chi-square test for categorical variables. We have added a new table in the manuscript: 2x2 contingency table and prevalence of possible PD.

Other minor points:

- Page 8, line 42: "The OR for an individual with “Possible PD” being in the “Possible IBD” group was ...". This is not a correct interpretation of the odds ratio.

We have reviewed the results by making the correction suggested. Thanks.

- The article summary states that matching by age and sex was performed, but abstract and article states that regression adjustment was done instead.

This study was not performed matching by age and sex, we have clarified it in the manuscript, thanks.

- What was the rationale for choosing the 65 age cutoff for stratification? Was this chosen a priori, or based on some observation in the data? Was age adjusted for linearly within these strata?

Our intention was to assess the risk of PD in the "senile" versus "presenile" phase. A priori we thought that there would be a reduction in risk of PE in younger patients with IBD exposed to aminosalicylates compared to those without IBD. Such a condition would delay the onset of PD, with the age factor being imposed with aging.

VERSION 2 – REVIEW

REVIEWER	Ubaldo Bonuccelli University of Pisa,Neurology Unit,Italy
REVIEW RETURNED	03-Mar-2019

GENERAL COMMENTS	This study is an excellent application of administrative data to the study of risk factors for a certain disease.In this study the relationship between the use of aminosalicylates as a tracer of individuals presenting with inflammatory bowel disease (IBD) and the use of antiparkinsonian drugs as tracer of Parkinson's disease (PD).The results suggest a protective role of minosalicylatesand/or IBD against PD development.

REVIEWER	Michael Sachs Karolinska Institute, Sweden
REVIEW RETURNED	07-Feb-2019

GENERAL COMMENTS	The authors have responded adequately to my comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 4

Reviewer Name: Michael Sachs

Institution and Country: Karolinska Institute, Sweden

Please state any competing interests or state ‘None declared’: None

Please leave your comments for the authors below

The authors have responded adequately to my comments.

Ok, thank you.

Reviewer: 3

Reviewer Name: Ubaldo Bonuccelli

Institution and Country: University of Pisa,Neurology Unit,Italy

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

This study is an excellent application of administrative data to the study of risk factors for a certain disease.In this study the relationship between the use of aminosalicylates as a tracer of individuals presenting with inflammatory bowel disease (IBD) and the use of antiparkinsonian drugs as tracer of Parkinson's disease (PD).The results suggest a protective role of minosalicylatesand/or IBD against PD development.

Ok, thank you.