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Abstract

The prognostic impact of inflammatory bowel disease (IBD), chronic inflammatory conditions consisting of ulcerative colitis (UC), and Crohn's disease (CD) on the risk of dementia has been poorly investigated. We evaluated the risk of dementia in IBD patients by a systematic review and meta-analysis of the available data. Three studies, enrolling 121.827 patients [14.839 IBD (12.1%) and 106.961 (87.7%) controls, respectively] were included in the analysis. Of these, 57.7% (*n* = 8.571) had UC, while 42.2% (*n* = 6268) had CD. The mean follow-up period was 21.3 years. A random effect model revealed an aHR of 1.52 (95% CI 1.04–2.020, *p* = 0.01; I2 = 91.1%) for dementia in IBD patients. Sensitivity analysis confirmed yielded results. Subjects having a CD showed an aHR for dementia of 1.48 (95% CI 1.07–2.03, *p* = 0.001, I2 = 68.9%), while the risk among those with a history of UC did not reach the statistical significance (aHR: 1.47, 95% CI 0.95–2.82, *p* = 0.81, I2 = 89.9%). IBD males had an increased risk of dementia compared to women. IBD patients and in particular those with CD have an increased risk of dementia in the long-term period.

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Introduction

Dementia represents a growing health concern worldwide [1]. It is known that patients with dementia have a high prevalence of comorbid medical conditions and related complaints, which directly influence the disease progression and relative outcome [2, 3]. A prompt identification of vulnerable populations at higher risk of dementia is key to identify those subjects who may benefit from early prevention and timely intervention. Over the last 2 decades, different studies have reported several medical conditions able to increase the risk of dementia. However, the prognostic impact of inflammatory bowel disease (IBD), chronic inflammatory conditions consisting of ulcerative colitis (UC), and Crohn's disease (CD) on the risk of dementia has been poorly investigated. The aim of the present manuscript is to evaluate the risk of dementia in IBD patients by a systematic review and meta-analysis of the available data.

Materials and methods

Study selection and data extraction

The study was performed in accordance with the Preferred Report Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Supplementary table S1) [4]. For this purpose, PubMed-MEDLINE and Scopus databases were systematically searched for articles, published in English language, from inception through September 15, 2021, using the following Medical Subject Heading (MESH) terms: "Inflammatory bowel disease" OR "IBD" AND "dementia". Inclusion criteria were: (i) studies enrolling subjects with a confirmed diagnosis of IBD, (ii) stratifying the population as UC and CD patients, and (iii) reporting the risk of dementia as adjusted hazard ratio (aHR) with relative 95% confidence interval. Conversely, case reports, review articles, editorials/ letters, and case series with less than 10 participants

as well as studies including duplicate populations, if any, were excluded. References from the included studies were screened to potentially identify other investigations meeting the inclusion criteria. Ethical approval and informed consent were not required, as this study did not directly enrol human subjects. For each assessed study, we extracted the overall, controls, UC and CD number of patients enrolled, the mean age, male gender, and the adjusted hazard ratio (aHR) for dementia in IBD patients as well as for UC and CD subjects' subgroups. The quality of the included studies was graded using the Newcastle–Ottawa quality assessment scale (NOS) [5].

Data analysis

From each study, the aHR with the related 95% confidence interval (CI) was pooled using a random effect model, while a forest plot was adopted to visually evaluate the results. Heterogeneity among studies was assessed using Higgins and Thomson I2 statistic where I2 values correspond to the following levels of heterogeneity: low (< 25%), moderate (25%–75%), and high (> 75%), respectively. Due to the low number of the included studies (< 10), small-study bias was not examined, as our analysis was underpowered to detect such bias. A predefined sensitivity analysis (leave-one-out analysis) was performed removing 1 study at the time, to evaluate the stability of our results regarding the risk of dementia in IBD subjects. To further appraise the impact of potential baseline confounders, a sub-analysis for UC and CD was performed. All metaanalyses were conducted using Comprehensive Meta-Analysis software, version 3 (Biostat, USA). A p value < 0.05 was considered statistically significant.

Results

Initial search resulted in 276 articles. After removing duplicates (n = 88) and applying our inclusion criteria, only 3 studies [6–8] enrolling 121.827 patients [14.839 IBD (12.1%) and 106.961 (87.7%) controls, respectively] were included in the analysis. Of these, 57.7% (n = 8.571) had UC, while

42.2% (*n* = 6268) had CD. The mean follow-up period was 21.3 years. Quality assessment showed that all studies were of moderate–high quality according to the NOS scale (Table 1). A random effect model revealed an aHR of 1.52 (95% CI 1.04–2.020, $p = 0.01$; I2 = 91.1%) for dementia in IBD patients (Fig. 1, Panel A). The relative funnel plot is shown in Supplementary Table S2; however, it cannot reassure about the presence of potential publication bias due to the lower number of available studies. To evaluate the robustness of the association results, we performed a leave-one-out sensitivity analysis by iteratively removing one study at a time and recalculating the summary aHRs, which remained stable (ranging between aHR: 1.31, 95% CI 1.09–1.33, $p < 0.001$ and aHR: 1.38, 95% CI 1.23–1.56, $p < 0.001$), indicating that our results were not driven by any single study. When the studies were stratified according to the type of IBD, those having a CD showed an aHR for dementia of 1.48 (95% CI 1.07–2.03, $p = 0.001$, I2 = 68.9%) (Fig. 1, Panel B), while the risk among those with an history of UC did not reach the statistical significance (aHR: 1.47, 95% CI 0.95–2.82, $p = 0.81$, I2 = 89.9%) (Fig. 1, Panel C). Intriguingly, IBD males had an increased risk of dementia compared to women.

Discussion

The results of the present analysis showed that patients affected by IBD, and especially those with CD, have a higher risk of dementia in the long-term period. However, due to the high heterogeneity observed, our results must be cautiously considered as a preliminary account on the impact of IBD on dementia. Probably, the heterogeneity observed is multifactorial. First, the limited number of studies satisfying the inclusion criteria and the relative few numbers of enrolled patients represent, per se, a potential source of heterogeneity. Second, inherited biases derived from the original investigations may have further contributed to the observed heterogeneity level. In fact, different levels of methodological quality and sampling bias by the competing risk of dementia may also have affected the results of this analysis. To this regard, also the retrospective design used by Zingel et al. [8] and therefore its lower methodological quality might have contributed to not firm results,

when compared with the other longitudinal investigations analysed. Moreover, the limited number of studies satisfying the nclusion criteria did not allow us to perform meta-regression for potential important confounders such as the length of IBD, the disease severity, previous surgical treatments, and type of dementia. Nonetheless, the sensitivity analysis performed confirmed the validity of our preliminary results. From a pathophysiological perspective, the mechanism promoting the risk of dementia in IBD patients has not been yet understood. Probably, the chronic systemic inflammation observed in IBD patients may represent a trigger for neuroinflammatory state, thereby driving microglia activation with consequent oxidative stress and misfolding proteins, mechanisms known to contribute to Alzheimer's disease [9]. The difference in dementia risk between CD and UC could be probably explained by the different systemic inflammatory mediator profile involved [10]; however, further dedicated studies are needed to elucidate the implicated inflammatory pathways. Furthermore, also the intestinal microbiota could represent another important mediator to linking IBD with the development of cognitive impairment/dementia. Indeed, the altered gut microbiota, which is commonly observed in IBD patients, can influence brain function and behaviour through the microbiota–gut–brain axis via various pathways such as increased amyloid-β deposits and tau phosphorylation, neuroinflammation, metabolic dysfunctions, and chronic oxidative stress [11, 12]. Our study has several limitations related to the design of the studied reviewed with all inherited biases and the numbers of investigation on the issue. In fact, only a few studies have analysed the relationship between IBD and dementia, limiting our results and conclusions. Moreover, the relatively high heterogeneity observed, which probably depends on the inclusion criteria as well as by the studies design, may have resulted in not firm conclusions. Finally, we cannot perform any analysis to evaluate the potential role of different risk factors for dementia, since they were not reported in the original investigations.

Conclusions

In conclusion, IBD patients and in particular those with CD have an increased risk of dementia in the long-term period. The potential benefits of early screening for dementia in these patients should be evaluated in the setting of randomized controlled trials.

Supplementary Information

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Declarations

Conflict of interest The authors declare that they have no conflicts of interest. Authors declare no competing financial, general, and institutional interests.

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