INPLASY PROTOCOL

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None declared.

Meta-analysis of the Risk of Allergic Rhinitis in Patients with Inflammatory Bowel Disease

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Review question / Objective: This meta-analysis aims to explore the risk of AR in patients with IBD.

Eligibility criteria: We used the following inclusion criteria: 1) The study was a case–control study, and there was a clear publication year. 2) The objective of the study was to investigate the risk of allergic rhinitis in patients with inflammatory bowel disease. 3) Subjects had inflammatory bowel disease/noninflammatory bowel disease (inflammatory bowel disease was diagnosed by the history of attack and clinical manifestations, supplemented by upper gastrointestinal radiography, endoscopy, colonoscopy, and gastrointestinal sampling). 4) The study was published in Chinese or English. We used the following exclusion criteria: 1) The number of cases of AR in IBD or non-IBD populations was not reported, or the reported data were duplicated. 2) The establishment of an experimental group and a control group in the study did not meet the standards. 3) The sample data were incomplete. 4) The article was a review, conference lecture papers, and republished literature. 5) The study reported on drug or animal experiments.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 May 2023 and was last updated on 19 May 2023 (registration number INPLASY202350077).

INTRODUCTION

Review question / Objective: This meta-analysis aims to explore the risk of AR in patients with IBD.

Rationale: There are many similarities between the pathogenesis of allergic diseases and IBD, but the exact mechanism underlying their relationship is still unclear. An imbalance between the immune system and gut microbiome in genetically susceptible individuals is a key factor. It has been established that changes in the gut microbiome may lead to the development of immune disorders, including atopic diseases (such as asthma, atopic dermatitis, AR, etc.) and IBD in

children with susceptible genotypes. The following describes the similar pathogenesis between IBD and AR. (1) Epithelial barrier: The human body needs to protect itself from various external stimuli, such as allergens, toxins, bacteria, fungi, viruses, and other pathogens. The human body has evolved protective epithelial barriers, such as those in the lung, skin, and intestine, to prevent external antigens from penetrating beyond the immune system barrier. The surfaces of the lungs, skin, and intestines are lined with epithelial cells that interact with environmental factors and immune cells. The gut and respiratory tract are derived from the original foregut and have a mucus-coated upper cortex that is constantly exposed to environmental pathogens. Airborne allergens enter the respiratory tract primarily through the nasal cavity but can also enter the mouth and deposit in the gastrointestinal tract. Some studies have shown that pollen that remains in the gut has some residual allergic activity. Therefore, the epithelium, together with the cellular immune system, plays a key role as a first-line physical barrier against external antigens. When these epithelial barriers are disrupted, external toxins, allergens, and contaminants can penetrate the body, inducing and promoting inflammation to defend against them. Therefore, defects in the mucosal barrier or epithelial cells can lead to an increase in the number of digestive system diseases (IBD, irritable bowel syndrome) and respiratory system diseases (AR, asthma, COPD). However, among all causes of mucosal inflammation, AR is the most common. (2) Microbial alterations: Microbial alterations could explain the association between AR and IBD. Studies have shown that the fecal flora of AR patients changes. Compared to healthy people, the intestinal microbiome composition and microbial function of AR patients changes significantly. This supports the hypothesis that the gut microbiome is involved in AR development. Similarly, the intestinal flora is different in IBD, and fecal microbiome biodiversity is significantly lower in IBD patients than in healthy controls. Other studies have also found that the microbiota of IBD patients is less stable than that of healthy individuals. Disruption of the microbiome affects the immune system, including the lungs, brain, and skin, producing products including the "gut-brain axis", "gut-lung axis", and "gut-skin axis". This results in an increased incidence of AR and IBD. (3) Immune disorders: Some researchers believe that the underlying complex pathological mechanism of IBD and atopic diseases (AR, asthma, atopic dermatitis, etc.) can be explained by immune disorders, including eosinophils, T helper cells (Th-2 and Th17) and transforming growth factor β (TGF-β). Recently, studies have found that interleukin (IL)-17-producing T helper cells (Th17) play a key role in defense. Pathogens are also involved in pathogenic immune-mediated induction and exacerbation responses, including IBD and AR. Th17 cells are induced by IL-1β, IL-6, and IL-23 and produce proinflammatory cytokines (TNF)-α, IL-17, and IL-22, including tumor necrosis factor, to recruit neutrophils and antimicrobial peptides to clear extracellular pathogens. However, Th17 cells are usually increased in the peripheral blood of patients with atopic diseases and are involved in lesions, including the airway and skin. Th17 cells may promote eosinophilic and neutrophilic inflammation in AR, which increases the development of AR. Th17 cells also promote immune-mediated responses and contribute to the development of IBD.

Condition being studied: The study found that the interaction of genetic and environmental risk factors and consequent epigenetic, microbiome, and immunological changes leads to the occurrence of AR in children. Sanitary conditions, allergens, infection levels, and lifestyle may all increase the prevalence of AR. Allergens associated with AR include pollen (trees, grass), mold, and indoor allergens (house dust mites and animal allergens). In addition, risk factors for AR include antibiotic use, air pollution, maternal and infant smoking, and vigorous exercise in adolescents. However, the risk factors for AR are not fully understood. Understanding the comorbidities of AR may contribute to the early detection and

treatment of AR, as well as further exploration of the pathogenesis of AR.

Inflammatory bowel disease (IBD) results from an interaction between genetic and environmental factors that influence the immune response. IBD includes idiopathic chronic inflammatory diseases of the gastrointestinal system, ulcerative colitis (UC), Crohn's disease (CD) and IBD unclassified (IBDU).

To date, many studies have been conducted on the comorbidity of IBD with other diseases, including allergies. The relationship between autoimmune diseases such as IBD and allergic diseases has long been a focus of attention. These diseases are similar in many ways, sharing risk factors (such as environmental factors, genetic factors, etc.), pathogenesis (microbiome, epithelial cell barrier, immune disorders, etc.), and treatments (treatment including the administration of immunomodulators and immuno-suppressants, such as steroids and cyclosporine). IBD is thought to be caused by an excessive immune response in the digestive system. They are also known to be associated with a variety of extraintestinal manifestations, including classic allergic diseases (asthma, atopic dermatitis, AR, etc.).

Both AR and IBD are mucosal inflammatory diseases characterized by immune dysregulation in the airways and gastrointestinal tract, respectively. In addition, the two diseases share several characteristics, including genetic predisposition and environmental exposure. AR may be a common extraintestinal manifestation in patients with IBD. However, whether IBD patients are at risk for AR is unknown. Therefore, we conducted a meta-analysis of patients with IBD and participants without IBD to understand whether there is a correlation between IBD and the development of AR and whether IBD patients are a risk population for developing AR.Both AR and IBD are mucosal inflammatory diseases characterized by immune dysregulation in the airways and gastrointestinal tract, respectively. In addition, the two diseases share several characteristics, including genetic predisposition and environmental exposure. AR may be a common extraintestinal manifestation in patients with IBD. However, whether IBD patients are at risk for AR is unknown. Therefore, we conducted a meta-analysis of patients with IBD and participants without IBD to understand whether there is a correlation between IBD and the development of AR and whether IBD patients are a risk population for developing AR.

METHODS

Search strategy: To identify relevant studies, a comprehensive literature search of publications was conducted in the following databases: PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), WanFang, medRxiv, bioRxiv, and METSTR. Abstracts of the major gastroenterological meetings (Digestive Disease Week, American Gastroenterological Association, and European Joint Gastroenterological Week) and thoracic meetings (American Thoracic Society, European Respiratory Society, and American College of Chest Physicians) were also included. The retrieval interval was from database inception to April 2023, and the publication language was either Chinese or English.

The following search terms were used in combination: "Inflammatory bowel disease", "Crohn's Disease", "ulcerative colitis", "IBD-type unclassification (IBDU）", "allergic rhinitis" and "hay fever".

Participant or population: The IBD group was the experimental group, and the non-IBD group was the control group.

Intervention: No intervention.

Comparator: No intervention.

Study designs to be included: Chinese and English databases, including PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), WanFang, medRxiv, bioRxiv, METSTR, and major gastroenterological meetings and thoracic meetings, were searched. Two evaluators independently screened the literature,

extracted data, and assessed the risk of bias in the included studies according to the inclusion and exclusion criteria. RevMan 5.4 was used to analyze the data.

Eligibility criteria: We used the following inclusion criteria: 1) The study was a case–control study, and there was a clear publication year. 2) The objective of the study was to investigate the risk of allergic rhinitis in patients with inflammatory bowel disease. 3) Subjects had inflammatory bowel disease/noninflammatory bowel disease (inflammatory bowel disease was diagnosed by the history of attack and clinical manifestations, supplemented by upper gastrointestinal radiography, endoscopy, colonoscopy, and gastrointestinal sampling). 4) The study was published in Chinese or English. We used the following exclusion criteria: 1) The number of cases of AR in IBD or non-IBD populations was not reported, or the reported data were duplicated. 2) The establishment of an experimental group and a control group in the study did not meet the standards. 3) The sample data were incomplete. 4) The article was a review, conference lecture papers, and republished literature. 5) The study reported on drug or animal experiments.

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Main outcome(s): IBD patients were more likely to develop AR than non-IBD patients, with high statistical heterogeneity ($X2=41.97$, $df=8$, $P<0.00001$, $I2=81\%$, OR=1.35 (95% CI 1.06–1.73) Z= 2.44, p= 0.01). The results showed p≤0.1 and I2≥50%, so the random effects model was used (See Figure 2). The results were statistically significant. From the results of our meta-analysis, we can conclude that IBD and AR are correlated. Compared with that in the non-IBD population, the incidence of AR is higher in IBD patients. It can be considered that IBD is correlated with the incidence of AR, and the presence of IBD leads to a higher risk of AR. This may provide a basis for predicting the risk of AR in IBD patients and exploring the mechanism underlying their comorbidity in the future.

Quality assessment / Risk of bias analysis: The NOS quality assessment tool was used to evaluate the quality of each study, with an average score of 7.2. The total score ranged from 7 to 8. All the cases in the study were mainly from hospitals, so the diagnoses were accurate. In terms of exposure factors, none of the nine studies reported response rates. In two of the studies, the quality assessment score was 8 points, mainly for control group selection. These two studies selected non-IBD patients in the same hospital. The other studies, which included only noninpatients, had scores of 7. In these studies, there was an inconsistency in the selection of control groups. In the 9 studies, the control group differed in terms of hospitalized staff (non-IBD patients with other diseases) patients' parents or partners, medical and paramedical staff, and healthy people.

Strategy of data synthesis: IBD patients were more likely to develop AR than non-IBD patients, with high statistical heterogeneity ($X2=41.97$, $df=8$, $P<0.00001$, $I2=81\%$, OR=1.35 (95% CI 1.06–1.73) Z= 2.44, p= 0.01). The results showed p≤0.1 and I2≥50%, so the random effects model was used (See Figure 2). The results were statistically significant.

Subgroup analysis: Eight of the studies were conducted in Europe, and one study was conducted in North America. In some studies, the patients were mainly

teenagers, with an average age of 10-15 years old, while in other studies, the patients were mainly middle-aged, with an average age of 38-48 years old; only the study by Timothy R. Card included all age groups. B. Hammer, D. P. Jewell and S. M. Pugh did not describe the age composition or the sex distribution of patients. The study by A. D'Arienzo only mentioned the sex distribution of patients in the control group. The mean age of the two groups and the sex distribution in the IBD group were not described.

Sensitivity analysis: We eliminated literatures successively, analyzed and combined the remaining literatures, and observed the changes in the combined results. We found that the results did not change significantly due to the changes in the number of studies, and this result was relatively robust.

Language restriction: The study was published in Chinese or English.

Country(ies) involved: China.

Keywords: Inflammatory bowel disease; Allergic rhinitis; Meta-analysis.

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