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Patients with inflammatory bowel disease have increased risk of autoimmune and inflammatory diseases

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World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7th, 14th, 21st, and 28th each month. The *WJG* Editorial Board consists of 1375 experts in gastroenterology and hepatology from 68 countries.

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ORIGINAL ARTICLE

Retrospective Study

Patients with inflammatory bowel disease have increased risk of autoimmune and inflammatory diseases

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Abstract

AIM

To investigate whether immune mediated diseases (IMD) are more frequent in patients with inflammatory bowel disease (IBD).

METHODS

In this population based registry study, a total of 47325 patients with IBD were alive and registered in the Danish National Patient Registry on December 16, 2013. Controls were randomly selected from the Danish Civil Registration System (CRS) and matched for sex, age, and municipality. We used ICD 10 codes to identify the diagnoses of the included patients. The IBD population was divided into three subgroups: Ulcerative colitis (UC), Crohn's disease (CD) and Both the latter referring to those registered with both diagnoses. Subsequently, odds-ratios (OR) and 95%CI were obtained separately for each group and their respective controls. The use of Bonferoni post-test correction adjusted the significance level to $P < 0.00125$. *P*-values were estimated using Fisher's exact test.

RESULTS

There were significantly more women than men in the registry, and a greater percentage of comorbidity in the IBD groups ($P < 0.05$). Twenty different IMDs were all significantly more frequent in the IBD group. Sixteen

were associated with UC versus twelve with CD. In both UC and CD ORs were significantly increased (P < 0.00125) for primary sclerosing cholangitis (PSC), celiac disease, type 1 diabetes (T1D), sarcoidosis, asthma, iridocyclitis, psoriasis, pyoderma gangrenosum, rheumatoid arthritis, and ankylosing spondylitis. Restricted to UC (P < 0.00125) were autoimmune hepatitis, primary biliary cholangitis, Grave's disease, polymyalgia rheumatica, temporal arteritis , and atrophic gastritis. Restricted to CD (P < 0.00125) were psoriatic arthritis and episcleritis. Restricted to women with UC (P < 0.00125) were atrophic gastritis, rheumatoid arthritis, temporal arteritis, and polymyalgia rheumatica. Restricted to women with CD were episcleritis, rheumatoid arthritis, and psoriatic arthritis. The only disease restricted to men (P < 0.00125) was sarcoidosis.

CONCLUSION

Immune mediated diseases were significantly more frequent in patients with IBD. Our results strengthen the hypothesis that some IMDs and IBD may have overlapping pathogenic pathways.

Key words: Immune mediated diseases; Ulcerative colitis; Risk; Prevalence; Registry; Chronic inflammatory diseases; Autoimmune diseases; Inflammatory bowel disease; Crohn's disease; Extraintestinal manifestations

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Core tip: Essential to inflammatory bowel disease (IBD) pathogenesis are environmental factors, altered gut microbiota and genetic susceptibility. The latter causing impairment of barrier function, autophagy, and Th1, 2 and 17 cell responses. Interestingly, these mechanisms are also thought important in other immune mediated diseases, as is the overlap of susceptibility genes. Besides the classic extraintestinal manifestations, we found a variety of immune mediated diseases to be more frequent in individuals with IBD. Physicians should be aware of this when treating these patients. Furthermore, these findings support the hypothesis that immune mediated diseases may have overlapping pathogeneses. Thus, understanding IBD might help us understand other immune mediated diseases and vice versa.

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INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are two distinct types of chronic inflammatory bowel diseases. The insight into etiology factors and the complex pathogenetic process is not yet fully understood. The diseases are often diagnosed in young individuals and recent studies report increasing incidences of both UC and CD, not only in Denmark but globally[1]. It has been suggested that inflammatory bowel disease (IBD) may be due to an inappropriate inflammatory response to the intestinal flora in genetically susceptible individuals. So far, several susceptibility genes have been identified[2]. Many of these are also found in other immune mediated diseases (IMDs), indicating overlaps between pathogenic pathways. The identified risk genes in IBD are involved in maintaining normal microbial gut homeostasis and adequate immune response[3,4]. Mutations in these may impair mechanisms essential to innate and adaptive immune response, *i.e.* weakened mucosal barrier, a decrease of antibacterial agents, impaired autophagy and antigen recognition. Mutations may also cause an imbalance of pro- and anti-inflammatory cytokines related to the regulation of Th1, 2 and 17 in particular[5]. CD is considered Th1 mediated thus characterized by interferon gamma, tumor necrosis factor alpha, and IL 12. UC is associated with a Th2 response where IL 4, 5, 10 and 13 are dominant. The Th17 response is present in both CD and UC but most pronounced in CD. It is characterized by IL 17 and 23 production. Th17 can also produce interferon gamma like Th1[5-8]. It is suggested that disturbances in these mechanisms may cause a loss of self-tolerance leading towards chronic inflammation or autoimmunity[9-12].

The gut microbiota of patients with IBD has been shown to contain less diversity, a reduced number of bacteria, and an altered microbial metabolite profile compared to healthy individuals[13]. Environmental factors, *i.e.* medication (antibiotics, non-steroid anti-inflammatory drugs and hormones), diet, geography, and previous infections might influence this[4]. A similar etiology is believed to exist in other IMDs, *i.e.* rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, type 1 diabetes (T1D), and celiac disease[14,15].

It has become clear, that patients with an existing IMD are more likely to develop other IMDs, this is more evident in females than in males[16]. Apart from the extraintestinal manifestations of IBD, little is known about the association between IBD and other IMDs.

Only a few large population based studies on the subject exist. The results of these suggest that IBD is associated with asthma, rheumatoid arthritis, psoriasis, multiple sclerosis, autoimmune thyroiditis, T1D, and vasculitis[17-22]. Different study designs, varying validity of diagnoses, population sizes and confounders, *i.e.* ethnicity, economic and social status, all make the findings of these studies difficult to interpret.

In Denmark healthcare is free and all contacts to hospitals are registered on an individual basis based on a civil registration number together with diagnosis

Table 1 Participants' demographic data

Variables	IBD	Control	UC	Control	CD	Control	Both[1]	Control
n	47325	92839	31066	60951	13343	26172	2916	5716
Female	54%	55%	53%	53%	58%	58%	56%	56%
Male	46%	45%	47%	47%	42%	42%	44%	44%
Mean age at entry, yr	53	53	55	55	49	49	47	47
Mean age at onset of IBD, yr	42	-	44	-	37	-	34	-
Mean duration of IBD at entry, yr	10	-	9	-	10	-	11	-
Comorbidity 0[2]	77%	83%	76.50%	82.00%	77%	85%	82%	87%
Comorbidity 1-2	18%	13.50%	18.00%	14%	18%	12%	15%	10%
Comorbidity ⩾ 3	5%	3.50%	5.50%	4%	5%	3%	3%	3%

[1]Patients registered with both CD and UC; [2]No. of comorbidities at onset of IBD according to the Charlson comorbidity index. CD: Crohn's disease; UC: Ulcerative colitis; IBD: Inflammatory bowel disease.

and procedural codes. This allows a unique access to information not confounded by economic and social status.

The aim of this study was to examine if IMDs are more frequent among patients with CD and UC compared to the background population.

MATERIALS AND METHODS

This was a cross-sectional study including all living patients with IBD who were matched with a control group to compare the point-prevalence of specific IMDs.

Identification of patients and controls

The Danish National Patient Registry include all contacts within the healthcare system both in-hospital, since 1977, and in outpatient settings since 1994. Data were retrieved on December 16, 2013 and included all patients alive registered with a diagnosis compatible with CD and UC. Patients were identified using the ICD 10 codes: CD K50.0-K50.9; UC, K51.0-K51.9). ICD 10 codes including "other" or "unspecified" were excluded to avoid inclusion of non-specific diseases and incorrect diagnosis codes.

The Danish Civil Registration System (CRS) includes all Danish inhabitants and each person has a unique 10-digit identification number. The CRS includes demographic data *e.g.* name, sex, date of birth, and death[23]. All IBD patients were paired (2:1) with random controls identified in the CRS and matched by sex, age (± 1 year) and municipality. Demographic data presented are based on data from the CRS.

The selected forty IMDs are all considered to be of either autoimmune or inflammatory origin. The same criteria were used for the IMDs. ICD 10 codes for the IMDs are listed in the Supplementary Table 1.

To assess comorbidity we used the Charlson comorbidity index which has been developed to estimate 1-year mortality in cancer patients. It is also useful in research to identify possible confounding diseases. It includes a number of systemic diseases associated with increased mortality, *i.e.* organ failure, AIDS, and cancer[24].

Ethics

This study was approved by the Danish Data Protection Agency (approval # 2013-41-1596). Approval from the Ethics Committee was not needed as this is a registry study.

Statistical analysis

The occurrence of IMDs was obtained separately for each group. Then OR and 95%CI were calculated. Fisher's exact test was used to calculate *P*-values.

We used the Bonferroni post-test correction to reduce the likelihood of false positives. We did 40 comparisons (the 40 IMDs investigated) and adjusted the significance level accordingly to $P < 0.00125$. Calculations was made using STATA version 13.0 (StataCorp LP, TX, United States).

RESULTS

A total of 47325 patients were alive and registered with IBD on December 16, 2013. A total of 92839 controls were identified.

CD was registered in 13343 patients, UC in 31066, and 2916 were registered with both diagnoses. A total of 92839 controls were found for the IBD group, 26172 for CD, 60951 for UC and 5716 for those with both diagnoses. Due to the matching criteria, five IBD patients had only one or no controls.

There was an excess of women in all IBD groups, most pronounced in CD ($P < 0.05$). The mean age at onset of disease was significantly higher in UC. Comorbidity was most frequent in those with either UC or CD ($P < 0.05$). See Table 1.

Twenty out of forty IMDs had significantly increased ORs in the IBD groups compared to their controls ($P < 0.00125$). Sixteen IMDs were associated with UC and twelve with CD. See Tables 2 and 3.

Seven of the IMDs were considered rheumatologic diseases, included ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, polymyalgia rheumatic, temporal arteritis, polyarteritis nodosa, and Churg

Table 2 Number of immune mediated diseases

Disease	IBD	Control	CD	Control	UC	Control	Both[1]	Control
Primary sclerosing cholangitis	257	4	35	1	192	2	30	1
Pyoderma gangrenosum	193	8	60	1	97	7	36	0
Autoimmune hepatitis	124	35	15	11	96	22	13	2
Celiac disease	280	92	133	30	132	58	15	4
Ankylosing spondylitis	431	151	189	32	201	102	41	17
Churg Strauss syndrome	14	5	4	1	8	4	2	0
Primary biliary cholangitis	71	32	11	6	53	25	7	1
Episcleritis	56	33	25	9	23	21	8	3
Iridocyclitis	419	295	148	82	230	188	41	25
Atrophic gastritis	60	47	16	11	42	34	2	2
Psoriasis	378	345	148	99	200	229	30	17
Polyarteritis nodosa	42	38	15	9	24	27	3	2
Rheumatoid arthritis	446	401	119	110	250	311	32	25
Type 1 diabetes	1682	1464	359	431	1002	1180	103	71
Sarcoidosis	141	122	29	38	79	94	14	9
Asthma	1140	981	337	363	568	695	76	82
Giant cell arteritis	193	156	37	46	116	141	3	6
Psoriatic arthritis	316	249	81	93	147	206	21	17
Grave's disease	817	581	141	207	394	561	46	49
Polymyalgia rheumatica	468	320	72	122	242	324	6	22

[1]Patients registered with both CD and UC. CD: Crohn's disease; UC: Ulcerative colitis; IBD: Inflammatory bowel disease.

Table 3 Odds-ratios for immune mediated diseases, in patients with inflammatory bowel disease

Disease	IBD	95%CI	UC	95%CI	CD	95%CI	Both[1]	95%CI
Primary sclerosing cholangitis	126.7[a]	47.2-340.3	189.5[a]	47.0-763.4	68.8[a]	9.4-502.6	59.4[a]	8.1-436.2
Pyoderma gangrenosum	47.5[a]	23.4-96.4	27.3[a]	12.7-58.7	118.2[a]	16.4-853.3	36/0[a,2]	
Autoimmune hepatitis	7.0[a]	4.8-10.1	8.6[a]	5.4-13.6	2.7[b]	1.2-5.8	12.8[a]	2.9-56.8
Celiac disease	6.0[a]	4.7-7.6	4.5[a]	3.3-6.1	8.8[a]	5.9-13.0	7.4[a]	2.4-22.3
Ankylosing spondylitis	5.6[a]	4.7-6.8	3.9[a]	3.1-4.9	11.7[a]	8.1-17.1	4.8[a]	2.7-8.4
Churg Strauss syndrome	5.5[a]	2.0-15.3	3.9[b]	1.2-13.0	-[c]		-[c]	
Primary biliary cholangitis	4.4[a]	2.9-6.6	4.2[a]	2.6-6.7	3.6[b]	1.3-9.7	13.8[b]	1.7-111.9
Episcleritis	3.3[a]	2.2-5.1	2.1[b]	1.2-3.9	5.5[a]	2.5-11.7	5.2[b]	1.4-19.8
Iridocyclitis	2.8[a]	2.4-3.3	2.4[a]	2.0-2.9	3.6[a]	2.7-4.7	3.2[a]	2.0-5.4
Atrophic gastritis	2.5[a]	1.7-3.7	2.4[a]	1.5-3.8	2.9[b]	1.3-6.2	-[c]	
Psoriasis	2.2[a]	1.9-2.5	1.7[a]	1.4-2.1	3.0[a]	2.3-3.8	3.5[a]	1.9-6.5
Polyarteritis nodosa	2.2[a]	1.4-3.4	1.7[b]	1.0-3.0	3.3[b]	1.4-7.5	-[c]	
Rheumatoid arthritis	1.8[a]	1.5-2.0	1.6[a]	1.3-1.9	2.1[a]	1.6-2.8	2.5[a]	1.5-4.2
Type 1 diabetes	1.7[a]	1.6-1.9	1.7[a]	1.6-1.8	1.7[a]	1.4-1.9	2.9[a]	2.2-3.9
Sarcoidosis	1.7[a]	1.3-2.2	1.7[a]	1.2-2.2	-[c]		3.1[b]	1.9-4.8
Asthma	1.7[a]	1.6-1.9	1.6[a]	1.4-1.8	1.8[a]	1.6-2.1	1.8[a]	1.3-2.5
Giant cell arteritis	1.6[a]	1.3-2.0	1.6[a]	1.3-2.1	1.6[b]	1.0-2.4	-[c]	
Psoriatic arthritis	1.5[a]	1.3-1.8	1.4[b]	1.1-1.7	1.7[a]	1.3-2.3	2.4[b]	1.3-4.6
Grave's disease	1.4[a]	1.3-1.6	1.4[a]	1.2-1.6	1.3[b]	1.1-1.7	1.9[b]	1.2-2.8
Polymyalgia rheumatica	1.3[a]	1.2-1.5	1.5[a]	1.2-1.7	-[c]		-[c]	

[a]$P < 0.00125$; [b]$P = 0.00125$-0.05; [c]$P > 0.05$; [1]Patients registered with both CD and UC; [2]No. of cases in IBD cohort/No. of cases in control cohort. CD: Crohn's disease; UC: Ulcerative colitis; IBD: Inflammatory bowel disease.

Strauss Syndrome.

Five IMDs were gastrointestinal including celiac disease, atrophic gastritis, primary sclerosing cholangitis, primary biliary cholangitis, and autoimmune hepatitis.

The remaining IMDs were T1D, Grave's disease, pyoderma gangrenosum, psoriasis, iridocyclitis, episcleritis, sarcoidosis, and asthma.

There was a trend towards significance (P = 0.00125-0.05) for Wegener's granulomatosis, chorioretinitis, vitiligo, lichen ruber planus, scleroderma, and multiple sclerosis.

Seven IMDs were only significant in women. While only one was restricted to men. See Table 4.

In general, the same pattern is seen in those registered with both CD and UC.

We did not observe any OR below one, neither did we record any cases of Sjögren's syndrome, inclusion body myositis, eosinophilic esophagitis, or autoimmune adrenalitis.

DISCUSSION

In this study, we documented an increased frequency

Table 4 Odds-ratios for immune mediated diseases restricted to either gender

Disease	Females	95%CI	Males	95%CI
IBD				
Episcleritis	3.6[a]	2.1-6.1	2.9[b]	1.4-6.1
Atrophic gastritis	3.5[a]	2.1-5.9	-[c]	
Polyarteritis nodosa	2.6[a]	1.5-4.5	-[c]	
Rheumatoid arthritis	1.9[a]	1.6-2.2	1.4[b]	1.1-1.9
Giant cell arteritis	1.7[a]	1.3-2.2	-[c]	
Psoriatic arthritis	1.6[a]	1.3-2.0	1.4[b]	1.1-1.9
Polymyalgia rheumatica	1.5[a]	1.3-1.8	-[c]	
Sarcoidosis	1.5[b]	1.1-2.2	1.9[a]	1.3-2.6
UC				
Atrophic gastritis	3.1[a]	1.7-5.8	-[c]	
Rheumatoid arthritis	1.7[a]	1.4-2.1		
Giant cell arteritis	1.7[a]	1.3-2.3	-[c]	
Polymyalgia rheumatica	1.6[a]	1.3-2.0	-[c]	
CD				
Episclerit	5.9[a]	2.4-15.0	4.5[b]	1.2-17.5
Rheumatoid arthritis	2.3[a]	1.7-3.0	-[c]	
Psoriatic arthritis	2.0[a]	1.3-2.8	-[c]	
Sarcoidosis	-[c]		3.2[a]	1.6-6.6
Both[1]				
Iridocyklitis	3.6[a]	1.9-6.8	2.7	1.2-6.2
Celiac disease	6.0[a]	1.9-18.6	3/0[b,2]	
Autoimmune hepatitis	17.9[a]	2.3-141.5	7.8[b]	0.9-69.8

[a]$P < 0.00125$; [b]$P = 0.0125-0.05$; [c]$P > 0.05$; [1]Patients registered with both CD and UC; [2]No. of cases in IBD cohort/No. of cases in control cohort. CD: Crohn's disease; UC: Ulcerative colitis; IBD: Inflammatory bowel disease.

of twenty IMDs in patients with IBD compared to matched cohorts.

Although most of the IMDs are considered to be Th1 mediated, UC was associated with more IMDs than CD. The presence of Th17 cells in UC and their ability to induce a Th1 response might explain this. Another explanation might be that certain susceptibility genes can act differently depending on the setting[25]. A gene might increase the risk of one disease while reducing the risk of others[25-27].

Extraintestinal manifestations

Ankylosing spondylitis, pyoderma gangrenosum, psoriasis, iridocyclitis, episcleritis, and primary sclerosing cholangitis (PSC) are all well described in IBD[28]. Thus the significant associations were expected. Except from PSC, these will not be discussed further.

Primary sclerosing cholangitis and gastrointestinal immune mediated diseases

PSC is predominant in men and most frequent in UC[29]. We found PSC to be associated with both types of IBD and both genders. Most striking is the association with CD which is less often described. Studies suggest that PSC is more frequent when colon is affected and a distinct subtype, PSC-IBD has been suggested[30-33]. This study does not include data on localization, severity or extension. Several PSC risk genes are shared with IBD and other IMDs[33,34]. Gene mutations influencing IL 10 signaling are identified in CD, UC and PSC. The absence of IL 10 can cause severe CD due to lack of Th1 and macrophage inhibition[33-35]. Interestingly, hepatobiliary inflammation is thought to be induced by microbial metabolites and changes in the microbiota and this inflammation is linked to the *FUT2* gene, which is also found in CD[33,34,36].

In contrast to most other studies[18,36,37], we found celiac disease to be more frequent in those with IBD regardless of type, as did another Danish study[16]. Other studies found IBD to be more common in patients with celiac disease but not vice versa[38-40]. Similarities and differences in pathogeneses might explain these conflicting results. Celiac disease is like IBD an inflammatory disorder of the intestine, often diagnosed in young individuals, more common in women, and Th1 mediated. Changes in microbiota and dysfunctional IL 18 receptor are also noted in both conditions[27,41]. Risk genes of celiac disease shared with CD relates to adaptive immunity while those shared with UC primarily relates to barrier function. Different from IBD is the absence of Th17 response, impaired autophagy and while important in celiac disease, IL 15 is not that important in IBD[41].

We found autoimmune hepatitis, primary biliary cholangitis, and atrophic gastritis to be more common in UC only. Again, results from previous studies conflict[16,18,21,42-45]. Little is known about the association with atrophic gastritis, which to our knowledge is unique to this study. Th1, 2 and 17 responses are important in IBD, PSC and primary biliary cholangitis pathogenesis. Primary biliary cholangitis and IBD have overlapping susceptibility genes, which is not the case with autoimmune hepatitis[46,47]. The pathogenesis of primary biliary cholangitis resembles those of autoimmune hepatitis and CD, dysfunctionalities in IL 12 signaling promotes a Th1 and possibly also a Th17 response, causing a granulomatous inflammation[47,48].

Endocrine diseases

UC is reported to occur more frequently in family members of patients with T1D[18,19,49]. However, three studies did not find any association[16,20,21]. This study found T1D associated with both UC and CD. Confounding due to treatment with corticosteroids is unlikely, as the mechanisms in steroid induced diabetes resemble those in type 2 diabetes[50,51]. Levels of IL 18 are elevated in CD and T1D, but not in UC. IL 18 causes a Th1 response and is likely to affect mucosal barrier function too[27,52]. PTPN2 is one of many shared risk genes[2,53]. It promotes beta cell apoptosis in T1D while causing intestinal barrier dysfunction, impaired autophagocytosis, and inhibition of Th17 in IBD[25,54]. Changes in the gut microbiota are also suggested to trigger T1D[27].

Data on autoimmune thyroiditis and IBD is sparse, similarities to IBD limited and only few risk genes overlap[55-57]. Restricted to UC only, we found OR significantly increased for Grave's disease. None was

detected for Hashimoto's thyroiditis. Similar results are reported in two other studies[18,58]. One study reports hypothyroidism more common in CD[19]. In addition, three other studies did not find any association at all[16,17,21].

Rheumatic diseases

Rheumatoid arthritis was associated with both UC and CD while psoriatic arthritis was restricted to CD. Previously published data support this[18,20,21,59]. The microbiome of the gut and skin are possible triggers in rheumatoid arthritis and psoriatic arthritis[60]. Both types of arthritis share characteristics with CD in particular. Th1 and 17 are essential in all three pathogeneses[2,61-64].

ORs for polymyalgia rheumatica and temporal arteritis were significantly increased in the IBD and UC group, not in CD. This is supported by one study while refuted by another[16,18]. Overlapping susceptibility genes suggest that Th1, Th17 and regulatory T cells are of importance to the pathogeneses[65].

ORs for Churg Strauss Syndrome and polyarteritis nodosa were significantly increased in the overall IBD group but not in the subgroups. The low number of cases calls for careful interpretation and future studies.

Other disorders

In this study, asthma was more common in both UC and CD. Both UC and allergic asthma are considered Th2 mediated. Also, a Th17 response is described in severe asthma[66]. Risk genes are associated with IL 13 and 17 production, dysfunctional regulatory T cells and regulation of Th1, 2 and 17 responses[26,66]. Studies have not found that asthma reduces the risk of IBD[67,68], rather the opposite seems more likely[17,18,20,21].

The association of sarcoidosis and IBD were restricted to UC and males with CD. Another study confirms the linkage to UC[18]. There is not much documentation for this association. The inflammation in sarcoidosis is similar to CD; granulomatous; Th1 and 17 driven; and mutations in NOD2 and IL 23 receptor gene are identified[2,69-71].

There were no cases of Sjögren's syndrome, inclusion body myositis, eosinophilic esophagitis, or autoimmune adrenalitis. This is unexpected. Some case reports have described the coexistence of Sjögren and primary adrenocortical insufficiency in IBD patients[16,72-74]. One case report describes eosinophilic esophagitis and CD[75]. While to our knowledge, no association between inclusion myositis and IBD has been reported. Although specific ICD 10 codes were used misclassification is still possible *e.g.* autoimmune adrenalitis might be registered as Addison's disease.

Strengths and limitations

The strength of this study is that it includes all patients alive with CD or UC in Denmark. The Danish population is homogenous regarding ethnicity and religion. Health care is free to all residents; thus, NPR is not biased by inclusion of specific hospitals, age groups, insurance policies, social, or financial status. As the general practitioners do not provide data, diseases not requiring hospital treatment could be underrepresented *i.e.* asthma, Grave's disease, Hashimoto's thyroiditis, and atrophic gastritis[76].

A limitation of the study is possible bias caused by varying validity of the ICD 10 codes. Only few Danish studies have addressed this issue. The average positive predictive value (PPV) of an ICD 10 diagnosis for any medical condition in the NPR varies from 65.5 % to 81%[76].

However, the completeness is 94% for both UC and CD while the PPV of UC and CD is 90% and 97% respectively[77].

The validity of T1D is like that of IBD, very high[24,78]. The PPV of asthma among hospitalized children is 85% while 65% among adults. However, a sensitivity analysis did not find the PPV in adults, low enough to nullify the hypothesis[79,80]. As a collective group the PPV of connective tissue diseases is reported as high[24]. The PPV of rheumatoid arthritis is low[81].

Despite varying validity of ICD 10 codes, most of our findings are in alignment with those of the studies using algorithms to increase the validity. Important to this study, is the occurrence of the classic extraintestinal manifestations which indicates that our results are not too biased.

Detection bias is another concern. Patients seen on regular basis by a physician such as those with IBD are more likely to be diagnosed.

To eliminate confounders like sex, age and geography in the IBD group, we used these as matching criteria. Information regarding smoking status was not available to us, thus no correction was made.

Another confounder is drug induced autoimmunity. A wide variety of drugs are suggested to induce autoimmunity. Among these are antibiotics, statins, methotrexate, thiopurines, and biological agents (anti-TNF-α agents)[82-88]. Biological agents, which are often used to treat IBD, ankylosing spondylitis, psoriasis, and rheumatoid arthritis, are paradoxically suggested to induce IMDs. No correction was made since we do not have data regarding patients' use of prescribed drugs.

While Bonferroni post-test correction reduced the risk of false positives, the risk of false negatives simultaneously increased. Knowing this, a low number of false positives were still preferred in this study.

In conclusion, our study emphasizes that immune mediated diseases are more frequent among patients with CD or UC. Our results strengthen the thesis of partially overlapping pathogeneses among some immune mediated diseases including IBD and emphasized the complexity of IBD pathogenesis. Our most important findings are the increased risk of

celiac disease and T1D in both UC and CD, but also the increased risk of primary sclerosing cholangitis in CD although not being limited to CD. Finally, when treating patients with UC or CD one should be aware of the strong association with other immune mediated diseases.

COMMENTS

Background

Extraintestinal manifestations in Crohn's disease (CD) and ulcerative colitis (UC) are well described. The authors aimed to investigate whether other immune mediated diseases were associated with inflammatory bowel disease (IBD).

Research frontiers

Most studies on the subject are small or case reports. Only few larger studies have been conducted. The authors aimed to estimate odds-ratios of developing an immune mediated diseases (IMD) in patients with IBD compared individuals without IBD.

Innovations and breakthroughs

This is one of few larger studies on the subject. It includes all patients alive with CD or UC in Denmark. Due to free health care to all residents the study is unbiased by inclusion of specific hospitals, age groups, insurance policies, social or financial status. The authors found several IMDs not considered classic extraintestinal manifestations to be significantly associated with IBD.

Applications

Physicians treating patients with IBD should obe aware of the increased risk of developing other IMDs than the classic extraintestinal manifestations. The findings support the hypothesis that shared pathogenic pathways among IMDs could exist.

Peer-review

It's a well-written and interesting manuscript.

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