Original Article

Concurrence of Inflammatory Bowel Disease and Multiple Sclerosis

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• *Objectives*: To quantify the coexistence of inflammatory bowel disease (IBD) and multiple sclerosis (MS) and to characterize the diseases when they coexist.

• *Patients and Methods*: In this retrospective study of medical records spanning 1950 through 1995, the diagnoses of Crohn disease (CD), ulcerative colitis (UC), and MS were based on review of inpatient and outpatient records by a gastroenterologist and a neurologist.

• *Results*: We identified 4 residents of Olmsted County, Minnesota, with IBD (3 UC, 1 CD) who had concurrent, clinically definite MS; all had mild neurologic disease with little disability. These comprised 1% of the IBD and 1.8% of the MS cohort. The CD patient had undergone terminal ileal resection; of the UC patients, 2 had pancolitis, and 1 had proctosigmoiditis. The observed prevalence of MS at onset of IBD was 3.7 times the expected (95% confidence interval, 0.8-10.8). We also reviewed the records of 32 referral patients with both diagnoses. Disability from MS was moderate at median follow-up of 8.5 years. By 15 years, ambulation was impaired in most patients. Neurologic disability was similar between patients with CD and UC.

• *Conclusions*: Concurrence of the 2 diseases was greater than expected. Although MS and IBD may share common predisposing factors, not enough information is available to speculate about possible mechanisms.

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CD = Crohn disease; CI = confidence interval; EDSS = Expanded Disability Status Scale; IBD = inflammatory bowel disease; MS = multiple sclerosis; SMR = standardized morbidity ratio; UC = ulcerative colitis

An association between inflammatory bowel disease (IBD) and multiple sclerosis (MS) has been reported. For example, in a follow-up study of 2261 women who underwent total colectomy and terminal ileostomy for ulcerative colitis (UC) in the United Kingdom, 10 patients were diagnosed with MS, yielding an estimated annual incidence of 18 per 100,000 persons compared with an expected incidence of MS in British women of only 5 per 100,000 persons.[1] Four other patients with IBD and MS have been reported, mostly women diagnosed with MS 5 to 8 years prior to presenting with Crohn disease (CD).[2-5] A possible familial association of IBD and MS has been noted in 17 families in southern Alberta.[6] Ten IBD patients—7 with CD and 3 with UC—had a relative with MS; conversely, of 7 MS patients, 3 had relatives with UC and 4 with CD. A comparable study in British Columbia found 27 families in which MS patients had a first-degree relative with IBD.[7]

Because of these reports, we performed a formal epidemiological survey in Olmsted County, Minnesota, where population-based cohorts of patients with CD[8,9] and UC[10] could be identified and the prevalence of MS[10] had been determined. A prior study in Olmsted County[11] failed to identify any association between MS and diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus, myasthenia gravis, or cancer. We also studied a population referred to the Mayo Clinic in Rochester, Minn, with concordant diagnoses of both IBD and MS to better assess the clinical spectra of the coexisting diseases.

PATIENTS AND METHODS

Population-based epidemiological research can be conducted in Olmsted County, Minnesota, because medical care is virtually self-contained within the community, and there are relatively few providers. Most subspecialty medical care is provided by the Mayo Clinic, which has maintained a common medical record system with its 2 affiliated hospitals (Saint Marys and Rochester Methodist) for more than 90 years. The Mayo Clinic dossier-type record contains both inpatient and outpatient data, and the diagnoses and surgical procedures recorded in these records are in-

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dexed. The index includes the diagnoses made for outpatients seen in office or clinic consultations, at emergency department visits, or in nursing home care, as well as the diagnoses recorded for hospital inpatients, at autopsy examination, or on death certificates. Medical records of the other providers who serve the local population, most notably the Olmsted Medical Group and its affiliated Olmsted Community Hospital, are also indexed and retrievable. Thus, the details of almost all medical care provided to the residents of Olmsted County are available for study.[12]

Study Subjects

Using this unique database (the Rochester Epidemiology Project), we identified all Olmsted County residents newly diagnosed with CD or UC from 1950 through 1995.[8,9,13,14] Potential patients were identified from the medical diagnostic index, surgical procedure index, death certificate diagnoses, autopsy diagnoses, and review of other available databases and registries.

Criteria for IBD.—The same diagnostic criteria used for previous retrospective epidemiological analysis of CD[8] and UC[9] in Olmsted County were applied. The diagnosis of CD required at least 2 of the following: (1) history of abdominal pain, weight loss, rectal bleeding, or diarrhea; (2) compatible endoscopic findings such as skip lesions, cobblestoning, fistulas, or perianal disease; (3) characteristic radiologic findings such as mucosal ulcerations, fistulas, or strictures; (4) characteristic gross features noted at laparotomy and surgical pathology, such as bowel wall induration, mesenteric lymphadenopathy, or serosal creeping fat/inflammation; or (5) histopathologic features of transmural inflammation or epithelial granulomas with no evidence of infectious organisms. The diagnosis of UC required evidence of mucosal inflammation and ulceration based on endoscopic, radiologic, surgical, or histologic findings. We also accepted findings of diffusely granular or friable mucosa on endoscopy, continuous involvement of the colon by endoscopy, radiographic or pathologic examination, and none of the features of CD. Patients suspected to have an infectious, antibiotic-associated, or ischemic etiology were excluded. Cases were required to have features consistent with IBD, after review of all available clinical, radiologic, endoscopic, and histologic findings. All charts were reviewed by a gastroenterologist to confirm the diagnoses of CD and UC.

Criteria for Neurologic Disease.—Patients were considered to have a diagnosis of MS based on neurologic history and findings on physical examination. All confirmed cases of MS were seen by Mayo Clinic neurologists, who made the diagnosis. Each chart was reviewed again by a neurologist and classified according to the criteria of Poser et al[15] as clinically definite or laboratory definite MS. Clinically definite patients must have had evidence of 2 distinct neurologic episodes due to separate lesions. Neurologic lesions found on magnetic resonance imaging of brain and/or spinal cord were accepted. Laboratory support consisted of oligoclonal bands or increased production of immunoglobulin G in the cerebrospinal fluid, provided that there was no active infection or collagen vascular disease. Only patients classified as definite MS were included in this study, adhering to the strict criteria used in previous epidemiological studies in Olmsted County.[10,11] For each patient, a Kurtzke Expanded Disability Status Scale (EDSS) score of 0 to 9.5 was assigned at the time of last complete neurologic assessment. On this scale, 0 is completely normal findings on neurologic examination, 1.0 to 3.5 is mild disability, 4.0 to 7.5 is moderate disability (gait limitation), and 8.0 to 9.5 is severe disability with confinement to wheelchair or bed.[16]

Data Analysis

The observed prevalence of MS at onset of IBD was compared with that of the expected prevalence (standardized morbidity ratio [SMR]). The expected number of cases was calculated by multiplying the age- and sex-specific prevalence rates of MS in this community[10] with the age- and sex-specific distribution of IBD patients at the time of diagnosis. The 95% confidence interval (CI) around the SMR was determined assuming a Poisson distribution.

RESULTS

Population-Based Risk of MS at IBD Diagnosis

We found 4 examples of MS and IBD (1 CD, 3 UC) among 474 Olmsted County IBD patients. All had only mild neurologic disabilities, and 3 had a diagnosis of MS prior to the onset of IBD symptoms. Table 1 summarizes these details. Based on the prevalence of these uncommon diseases among Olmsted County residents generally (Table 2), only 0.81 MS case would have been expected (SMR, 3.7; 95% CI, 0.8-10.8). When the sexes were considered separately, the SMR was 8.7 (95% CI, 1.1-31) for men and 1.7 (95% CI, 0.0-9.6) for women. This analysis excluded 1 instance of MS with an onset of neurologic symptoms after the diagnosis of IBD (patient 1 in Table 1).

Olmsted County residents with IBD had mild MS (EDSS, 1.0-1.5) after a median follow-up of 7.5 years (range, 6-13 years). With respect to Olmsted County, 1.8% of MS cases had a comorbid diagnosis of IBD.[17]

Referral Population of Patients With IBD and MS

We also identified by the same criteria 32 patients (9 men and 23 women) with concurrent diagnoses of IBD and MS who had been referred to Mayo Clinic from outside

Table 1. **Clinical Features of 4 Patients in Olmsted County, Minnesota, With IBD and MS***

Patient/sex	GI presentation	Neurologic symptoms	Neurologic disability (EDSS)
1/F	Age 21 y, diagnosis of UC, treated with sulfasalazine; age 27 y, 2 flares of UC	Age 27 y, optic neuritis; age 32 y, leg paresthesias, abnormal MRI, leading to diagnosis of MS; age 33 y, recurrent optic neuritis and leg ataxia; age 45 y, no disability	None (1.0) 13 y after diagnosis of MS
2/M	Age 38 y, active colitis (colonoscopy), treated with prednisone and mercaptopurine	Age 29 y, optic neuritis; age 36 y, diagnosis of MS; age 41 y, fluctuating ataxia, spastic monoparesis; age 43 y, mild leg spasticity	Age 43 y, mild (1.5) 7 y after diagnosis of MS
3/F	Age 29 y, active colitis (colonoscopy), treated with sulfasalazine	Age 25 y, diagnosis of MS after paresthesia and dysequilibrium; age 28 y, recurrent paresthesia; age 33 y, no further symptoms	None (1.0) 8 y after diagnosis of MS
4/M	Age 28 y, emergent appendectomy, found to have Crohn ileitis; no medications	Age 28 y, Lhermitte sign, diagnosis of MS after abnormal MRI and spinal fluid findings; age 32 y, no further symptoms	None (1.0) 4 y after diagnosis of MS

*EDSS = Expanded Disability Status Scale; GI = gastrointestinal; IBD = inflammatory bowel disease; MRI = magnetic resonance imaging; MS = multiple sclerosis; UC = ulcerative colitis.

Olmsted County. This group consisted of 22 patients with UC (median age at onset, 32 years; range, 6-68 years), most of whom had severe disease. Sixteen patients had pancolitis, and 12 had undergone colectomy. Ten patients had CD (median age at onset, 33 years; range, 12-61 years), 3 of whom had undergone surgical resections. In 2 patients, the extent of IBD was not well documented. The neurologic symptoms began with equal likelihood before or after the gastrointestinal symptoms, from 38 years before to 32 years after the symptoms of IBD (median, 0.5 year before IBD symptoms). The mean disability score was 3.5 (fully ambulatory, mild disability; range, 1.0-9.0) after a median follow-up of 8.5 years (range, 1-48 years). Patients with CD and UC had similar outcomes. For patients followed up for more than 15 years, most had moderate disability, impairing ambulation to different degrees.

DISCUSSION

We found a likely association between IBD and MS in a population-based cohort of Olmsted County residents with IBD. In the IBD cohort, 4 (0.8%) of 474 cases developed MS. Analysis of a larger referral cohort with concurrent MS and IBD suggests that common risk factors underlie this association, as opposed to concurrent involvement of multiple organs by a single disease process. Since the prevalence of MS in Olmsted County is only 160 per 100,000 persons,[10] we expected no cases or, at most, 1 case (actually 0.81) of MS among this cohort of 474 IBD patients. Using a person-year model, the overall SMR of 3.7 for prevalence of MS at the time of diagnosis of IBD exceeds that for MS at the time of diagnosis of other disorders such as diabetes mellitus (relative risk, 2.5)[11] or rheumatoid arthritis (relative risk, 1.8),[11] which are not thought to be associated with MS. Olmsted County has higher rates for CD and MS than are seen elsewhere,[17-20] probably due in part to more complete ascertainment in the region, with its ready access to specialists. We applied strict criteria for each disease, to err conservatively in the diagnosis of comorbidity. Of note, socioeconomically Olmsted County (96% white in 1990) resembles the US white population.[12]

Many referral patients with IBD had a mild to moderate course of MS, but the 4 Olmsted County patients exhibited no or minimal symptoms and were only mildly disabled. Thus, Olmsted County population surveys include many mild examples of MS, and these patients often work full-time,[17] whereas referred patients probably exhibit a bias for more severe disease. Focal white matter brain lesions with no or minimal neurologic symptoms have been noted in IBD patients.[21,22] However, our data do not suggest that central nervous system involvement is an extra*intestinal* manifestation of IBD, since the onset of neurologic symptoms was usually quite remote from and equally likely to precede or follow the onset of IBD in the large referral group.

Table 2. **Prevalence of MS Among Olmsted County, Minnesota, Residents at First Diagnosis of IBD, 1950-1995***

Age group (y)	Prevalence of MS (per 100,000)	No. of IBD cases	Expected No. of MS cases	Observed No. of MS cases	SMR (95% CI)
Men					
<15	...	14	...	...	...
15-24	26.6	58	0.02	0	0.0 (0.0-239)
25-34	71.2	61	0.04	1	23 (0.6-128)
35-44	124.2	46	0.06	1	18 (0.4-97)
45-54	150.2	25	0.04	0	0.0 (0.0-98)
55-64	292.6	21	0.06	0	0.0 (0.0-60)
≥65	98.7	17	0.02	0	0.0 (0.0-242)
Subtotal		242	0.23	2	8.7 (1.1-31)
Women					
<15	...	8	...	...	...
15-24	48.0	62	0.03	0	0.0 (0.0-124)
25-34	167.9	66	0.11	1	9.0 (0.23-50)
35-44	432.6	43	0.19	0	0.0 (0.0-20)
45-54	431.8	24	0.10	0	0.0 (0.0-36)
55-64	675.7	14	0.10	0	0.0 (0.0-39)
≥65	369.1	15	0.06	0	0.0 (0.0-67)
Subtotal		232	0.58	1	1.7 (0.0-9.6)
Total	474	0.81	3	4	3.7 (0.8-10.8)

*CI = confidence interval; IBD = inflammatory bowel disease; MS = multiple sclerosis; SMR = standardized morbidity ratio.

Both IBD and MS are chronic indolent or recurrent organ-specific inflammations. They affect predominantly young adults, occur more frequently in developed countries at Northern latitudes, and presumably have polygenic hereditary and environmental susceptibility factors.[23,24] In addition, both respond to drugs that impair cell-mediated immunity such as corticosteroids, azathioprine, and possibly cyclosporine.[25-27] Moreover, sulfasalazine, which has been used to treat IBD for 50 years, may suppress experimental autoimmune encephalitis, an animal model for MS.[28-30] However, in a multicenter, placebo-controlled MS trial, sulfasalazine had beneficial effects during the first 2 years of treatment but made no difference to the longer-term progression of disability. Larger population-based studies are needed to confirm an increased risk of MS in IBD patients. Additional evaluation of comorbid cases will help elucidate the genetic or environmental factors predisposing certain individuals to both diseases.

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