The concurrence of inflammatory bowel disease and multiple sclerosis

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ABSTRACT

Inflammatory bowel disease and multiple sclerosis are both autoimmune diseases with an unknown etiology. It has previously been reported that the concurrence of both diseases in one family or patient is much higher than the expected value in the normal population.

In this article we describe four patients with inflammatory bowel disease and concurrent multiple sclerosis that were seen at the VU University Medical Center in Amsterdam. Two of these patients suffered from Crohn’s disease and two from ulcerative colitis. We also review the medical literature on the concurrence of IBD and MS and in order to get a better insight into these medical disorders we have revised the existing hypothesis explaining the association. It is likely that genetic factors play an important role in the predisposition and concurrence of these chronic diseases. Similar pathophysiological mechanisms may explain the response to immunomodulatory therapy. However, the course of inflammatory bowel disease and multiple sclerosis ran independent of each other and some immunoregulatory agents are good for one condition but may be deleterious for the other.


INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic inflammatory disorders of the gastrointestinal tract of still unknown etiology and consist of two main entities: ulcerative colitis (UC) and Crohn’s disease (CD). The key feature is an abnormal intestinal immunological response to an environmental factor in genetic susceptible people. Although there are many similarities between CD and UC, marked differences in disease localization and histological feature exist (1-3).

Multiple sclerosis is the most common inflammatory demyelinating disorder of the central nervous system (CNS) and disease etiology is also still unclear, whereas autoimmunity is used as the most widely accepted hypothesis (4,5). The disease is characterized by multiple sclerotic lesions called plaques, which can be found in the brain and the spinal cord (4). The demyelination results in an inefficient signal transduction, leading to neurological impairments (6).

Similar to IBD an abnormal immune response is present in MS patients. In both diseases activated cells of the immune system can be identified in pathologic lesions. Another similarity related to the immunological bases of the diseases is the importance of immunoregulatory and immunosuppressive therapy as a treatment strategy (7,8).

MS and IBD share similar epidemiological traits, both occur more frequently in developed countries at Northern latitudes (9-11). Shared genetic factors and environmental factors are both thought to confer susceptibility for these disorders resulting in their concurrence in a patient or in families (12,13).

Up till now, several studies have described an association between IBD and MS (14-19). Rang et al. reported the first association between IBD and MS in 1982. They investigated the incidence of breast cancer in women who had undergone colectomy for UC, CD or familial polyposis and they unexpectedly found an increased prevalence of MS among the UC patients, which was three times higher than in the normal population (14).

In 1986, Minuk and Lewkonia also reported an association of MS and IBD. They observed the concurrence of both diseases in southern Alberta, Canada and found 17 instances of coexistence of the diseases among families in a regional population of about 1 million, which were more than expected. At that time, published prevalence rates for MS and IBD in southern Alberta were 30-80 per 100,000 and 40-100 per 100,000 respectively. Interestingly, no patient with both diseases was found in these families with MS and IBD (15). Sadovnick et al. in 1989 confirmed the coexistence of MS and IBD in 27 families from Vancouver, British Columbia and reported 4 patients with both MS and IBD (2 with concurrent UC and 2 with
concurrent CD) out of a population of 3 million. This is again an increased rate, because only 1 per million would be expected (16).

Kitchin et al. reported in 1991 a case report about the occurrence of CD in a patient with well-established MS. Her son also developed CD, but no MS (17). One year later Purrmann et al. described a 29-years-old woman who developed MS in 1983, at the age of 22 and CD in 1989, at the age of 28 (18).

Also in France, 4 patients (0.5%) with both diseases were found in a personal and familial histories search that was undertaken in 832 patients with Crohn’s disease who were seen consecutively in the same hospital clinic between 1974 and 1994 (20).

Kimura et al. and Constantinescu et al. published the most recent reports about the concurrence of IBD and MS in 2000. The first group of authors performed a population based epidemiological study in Olmsted County in Minnesota, U.S.A. Four hundred and seventy patients with either UC or CD were identified. Among them 4 (1 CD, 3 UC) suffered from MS as well. All had only mild neurological disabilities and 3 had diagnosis of MS prior to the onset of IBD symptoms. Based on the prevalence of these disorders only 0.81 MS cases would be expected and almost 5 times the expected prevalence was observed (19). In the UK, two patients developed the first manifestations of multiple sclerosis while on long term (3.5 and 10 years, respectively) treatment with azathioprine for Crohn’s disease (21).

In this study we describe four patients with MS and concurrent IBD, which have been diagnosed since 1982 at the department of gastroenterology and neurology of the VU University Medical Center (VUmc) in Amsterdam (Table I) and review the literature and current hypothesis to explain the association.

PATIENTS

The first patient, a 35 years old Caucasian woman, was seen in 1973. The first symptoms of a demyelinating disease occurred at the level of the spinal cord. She suffered from paraesthesias starting in both feet and expanding to the chest level. The diagnosis of MS was made elsewhere based on the clinical symptoms and characteristic abnormalities –elevated IgG index and the presence of oligoclonal bands at isoelectric focusing – in the cerebrospinal fluid (CSF). During the next 25 years, the disease ran a relatively mild relapsing remitting (RR) course with occasional relapses and complete remissions. In 1990 she was seen at the outpatient clinic of the department of Neurology at the VUmc because the clinical picture seemed to have changed into a gradually progressive disease course. It was concluded that at that time she suffered from secondary progressive (SP) MS, but disability due to MS was mild. In subsequent years, she visited the outpatient clinic at regular intervals. Disease progression over the years was limited. In 1997, a magnetic resonance imaging (MRI) scan of the brain revealed T2 abnormalities in both hemispheres corresponding to the diagnosis of MS, but no infratentorial lesions were seen.

The patient presented at the department of gastroenterology in March 1997, with diarrhea and lower abdominal pain of two weeks duration. A few days later, she was hospitalized with severe abdominal pain, rectal blood loss and diarrhea, clinical signs compatible with ulcerative colitis. A CT scan showed no abdominal masses or other intra-abdominal pathology. Sigmoidoscopy at that time showed edema and ulceration of the mucosa of the colon up to 25 cm. Histological evaluation of the biopsy specimens confirmed chronic and actively inflammation with infiltration of lymphocytes and granulocytes in the mucosa and the submucosa. In one of the biopsy specimens’ ulceration of the colon epithelium was observed with formation of granulation tissue. The plasma cell typing showed an increase in IgA and IgG compatible with the diagnosis of ulcerative colitis. After excluding pathogens, glucocorticosteroid therapy was started, in addition to Mesalazine. These measures were sufficient to control the disease.

In August 2000 she had an exacerbation of the ulcerative colitis and further evaluation investigations revealed carcinoma of the ovary, confirmed at laparotomy. She died of cardiovascular failure in October of that year at the age of 63 years.

The second patient, a 39 year old woman presented in February 1996 at the outpatient clinic of the department of Neurology because of sensory complaints leading to a clinical diagnosis of partial transverse myelitis. MRI showed spinal cord abnormalities and characteristic lesions in the brain. An elevated IgG index and oligoclonal band was observed in the CSF. She visited the outpatient clinic at regular intervals and relapses were observed in the course of the disease. The patient died from pneumonia in March 1998 at the age of 40 years.

The third patient, a 52-year old woman, was first seen at the outpatient clinic of the department of Neurology in 1987. She had already been diagnosed with MS in 1981. In 1991 she was admitted to the hospital with severe abdominal pain and diarrhea. The disease had started with a history of abdominal pain and weight loss. In the course of the disease she had suffered 2 relapses of MS and experienced increased bowel symptoms. A CT scan of the abdomen showed an ileocecal abscess with peritonitis. She visited the outpatient clinic at regular intervals and relapses were observed in the course of the disease. The patient died from pneumonia in January 1995 at the age of 56 years.

The fourth patient, a 21-year old woman, was diagnosed with MS in 1988. At the age of 23 she was admitted to the hospital with severe abdominal pain and diarrhea. The disease had started with a history of abdominal pain and weight loss. A CT scan of the abdomen showed an ileocecal abscess with peritonitis. She visited the outpatient clinic at regular intervals and relapses were observed in the course of the disease. The patient died from pneumonia in January 1995 at the age of 25 years.

In Table I, the characteristics of the four patients are shown.

Table I. Patients with IBD and MS (VU University Medical Centre, Amsterdam)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>Age of diagnosis MS</th>
<th>Age of diagnosis IBD</th>
<th>Type of IBD</th>
<th>Time between onset MS &amp; IBD</th>
<th>Classification</th>
<th>Vienna</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (†10-4-2000)</td>
<td>65/f</td>
<td>35</td>
<td>60</td>
<td>UC</td>
<td>25</td>
<td>III</td>
<td>A1, L2, B3</td>
</tr>
<tr>
<td>2</td>
<td>39/f</td>
<td>33</td>
<td>35</td>
<td>CD</td>
<td>2</td>
<td>A1-2, L2, B3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>52/f</td>
<td>39</td>
<td>47</td>
<td>CD</td>
<td>8</td>
<td>A1-2, L2, B3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>39/f</td>
<td>22</td>
<td>29</td>
<td>UC</td>
<td>7</td>
<td>III</td>
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Average age at diagnosis MS: 31.8 (range 22-39) Average age at diagnosis IBD: 40.8 (range: 29-60)
bands at CSF examination confirmed the diagnosis of MS (April 1966). In this patient, the disease is clinically characterized by a mild relapsing remitting course. Disability is low with 2.0 as the highest EDSS score at follow-up so far.

Two years later (February 1998), she presented with diarrhea accompanied with severe blood loss. A colonoscopy showed large and smaller ulcers in the sigmoid. The biopsy specimens showed a colon mucosa with focally increased inflammatory infiltrate with some granulocytes and signs of extensive chronic active inflammation. Plasma cell typing showed an increased number of IgM positive plasma cells. Based on these findings Crohn’s disease was diagnosed. A relapse occurred in September, colonoscopy showed a swollen mucosa of the ascending, descending and transverse colon. In addition, histopathology confirmed the diagnosis of Crohn’s disease based on the presence of granulomas and focal inflammation. She was initially treated with glucocorticosteroids for several months and therapy with azathioprine was started as maintenance therapy. The patient is still in remission.

Patient 3 is a woman born in 1950. Bowel complaints started in 1984 at the age of 34, when she had 3 surgical interventions for an anal fistula. Thereafter, the patient suffered from incontinence for watery stools. Five years later, in February 1989, she was seen at the Neurology department with a disorder at the spinal level, manifesting as sensory complaints. A spinal cord MRI in that year confirmed the suspicion of a demyelinating disorder. A brain MRI at that time showed no clear abnormalities, but no infratentorial lesions. In CSF, oligoclonal bands were reported. A MRI scan of the thoracic spinal cord showed no abnormalities but brain MRI revealed three infratentorial lesions. In CSF, oligoclonal bands with an elevated IgG index were found. In November that year the diagnosis of MS was definite and a mild relapsing remitting course has followed.

In February 1993, she had complaints of frequent diarrhea with severe blood loss in the feces for several months with a worsening since January. The fecal cultures were negative and she suffered no weight loss. A colonoscopy revealed a hyperemic, granular mucosa, limited to the rectum. Mesalazine was prescribed. One month later, she returned to the hospital with severe bloody diarrhea and fever of 38 °C. Colonoscopy revealed an edematous, vulnerable mucosa, which was diagnosed as a pancolitis. The dose of Mesalazine was increased and the patient complaints improved in a week.

In April 1993 that year a colonoscopy revealed edematous and easily bleeding mucosa, biopsy specimens showed a light active focal colitis, compatible with Crohn’s disease. The mesalazine therapy was continued until March 1996 when the bleeding returned. Sigmoidoscopy revealed an edematous and hemorrhagic rectum. The biopsy specimens were compatible with ulcerative colitis. The mesalazine therapy was continued in a higher dose. A sigmoidoscopy one month later showed no macroscopic alterations, although biopsy specimens showed signs of inflammation, edematous bleedings and small ulcers. In addition to the mesalazine, steroids were prescribed too. But in April 1996 she had to be hospitalized. She had frequent diarrhea with blood loss, mucus, fever and severe upper abdominal pains. A colonoscopy revealed a severe inflamed mucosa of the rectum with many ulcers and purulent spots. Spontaneous bleedings was also present. Culture of the feces was positive for Campylobacter jejuni. The biopsy specimens showed a severe and active pancolitis, complicated with the infection of C. jejuni. A subtotal colectomy with an ileostomy was performed leaving the rectum in situ. Pathology confirmed the diagnosis of ulcerative colitis. After surgery, during the period of recovery the patient developed an ileus. A laparotomy was performed, the rectum was inflamed and removed cause of ongoing relapses accompanied by increasing disability. In October that year, she had severe constipation and was incontinent for urine and feces.

In December 1999, she had a severe exacerbation of Crohn’s disease that required hospitalization and treatment with intravenous steroid therapy. Bone densitometry revealed osteoporosis of the lumbar column and the hip.

In June 2000, MS symptoms exacerbated but the Crohn’s disease is quiescent. At the last visit to the neurological outpatient clinic her EDSS score was 5.5.

The fourth patient described in this study is a female born in 1963. In July 1986, the first MS complaints, consisting of sensory symptoms at the level of the spinal cord, were reported. A MRI scan of the thoracic spinal cord showed no abnormalities but brain MRI revealed three infratentorial lesions. In CSF, oligoclonal bands with an elevated IgG index were found. In November that year the diagnosis of MS was definite and a mild relapsing remitting course has followed.

In April 1993 that year a colonoscopy revealed edematous and easily bleeding mucosa, biopsy specimens showed a light active focal colitis, compatible with Crohn’s disease. The mesalazine therapy was continued until March 1996 when the bleeding returned. Sigmoidoscopy revealed an edematous and hemorrhagic rectum. The biopsy specimens were compatible with ulcerative colitis. The mesalazine therapy was continued in a higher dose. A sigmoidoscopy one month later showed no macroscopic alterations, although biopsy specimens showed signs of inflammation, edematous bleedings and small ulcers. In addition to the mesalazine, steroids were prescribed too. But in April 1996 she had to be hospitalized. She had frequent diarrhea with blood loss, mucus, fever and severe upper abdominal pains. A colonoscopy revealed a severe inflamed mucosa of the rectum with many ulcers and purulent spots. Spontaneous bleedings was also present. Culture of the feces was positive for Campylobacter jejuni. The biopsy specimens showed a severe and active pancolitis, complicated with the infection of C. jejuni. A subtotal colectomy with an ileostomy was performed leaving the rectum in situ. Pathology confirmed the diagnosis of ulcerative colitis. After surgery, during the period of recovery the patient developed an ileus. A laparotomy was performed, the rectum was inflamed and removed
DISCUSSION

The isolated reports of the concurrence of IBD and MS, with the four cases reported here and the increased prevalence in population-based studies have confirmed a link between these two autoimmune diseases (14-19).

Different hypotheses have been postulated to explain the greater than expected concurrence of IBD and MS in a family or in the same patient. Since both diseases are multifactorial and polygenic, Minuk et al. postulated that one or more loci contributing to CD might also confer susceptibility for MS. Although, these authors have said that it is unlikely that loci from the major histocompatibility complex (MHC) confer susceptibility for both diseases (15), there is evidence that HLA–DR2 or a closely related, yet unidentified gene maybe involved in the link between UC and MS. About 40% of patients with UC (22-28) and MS (29-31) carry this antigen.

Several genetic studies, including whole genomic screen studies, investigated susceptibility regions related to IBD or MS (32-39). The first genome screen in CD was reported by Hugot et al. in 1996 (32). They identified four markers; three were on chromosome 1 and one on chromosome 16. These findings were successfully replicated by other studies (40,41). Genotyping led to the localization of a single gene, the IBD1 gene identified as the CARD15/NOD2 gene. Polymorphisms within this gene showed to be associated with CD (18,42). Many studies have found that several chromosomes have probably genes involved in the susceptibility for UC, for example, an IBD2 gene possibly exist on chromosome 12 (36,43,44). Weak evidence was found for linkage between chromosome 6 and 2 and UC (43). The genes of the MHC are intensively investigated in genetic studies in IBD and it is now well accepted that the genes of this region influence not only disease susceptibility but also disease behavior (43,45-47).

The only consistent relation observed in the genetics of MS is the allelic association with products of the MHC on chromosome 6p21 (37). The strongest associations are with the HLA class II antigens (37,48,49). Multiple sclerosis genomic screens have been performed in different countries. Highest non-parametric linkages (NPL) score was found on chromosome 17q11 (NPL score 2.58). Another region with a NPL score greater than 2 was the HLA region (33). However, in the field of MS, several genome screens have been completed, but no major disease gene has been found (33,34), although recently a whole-genome screen performed on nine members of a consanguineous family where the index case, three of her siblings and her daughter, all of whom have been diagnosed with definite MS found evidence of linkage (LOD score of 2.29) on the long arm of chromosome 9 (50). There is consensus, that MS like IBD is a multifactorial and polygenic disease. As Vyze and Todd have eloquently written: “this single characteristic (incomplete risk conferred by any single allele) is the main reason why most common diseases such as autoimmune conditions are not inherited in a simple Mendelian way, but instead have a complex or unknown mode of inheritance” (51).

Purrmann et al. have intensively studied the candidate genetic markers for IBD and MS. They suggest that susceptibility loci for both diseases are associated with HLA haplotypes A3, B7, DR2 and A2, B12 (B44), Cw5 respectively, but as far as we know at this moment, there are no common loci in the MHC region that confer susceptibility for both diseases. Purrmann et al. also pointed towards the possible common influence of environmental factors supported by the fact that IBD and MS occur most frequently in the highly developed countries of the northern hemisphere, as well as in Australia and New Zealand. They conclude that MS and CD may have common exogenous triggers that, depending on the genetic makeup, may be responsible for the manifestation of either MS or CD (18).

Sadovnick et al. supported this hypothesis, but they added the idea that a generalized problem with the immune system, could also result in familial aggregates of diseases such as MS, IBD, but also diabetes, lupus erythematosus and rheumatoid arthritis (16).

A different hypothesis has been proposed by Kitchin et al. (17). The shared immune defect is supported by the presence, in both diseases, of activated cells of the immune system in the pathological lesions and the positive effect of immunosuppressive therapy. Therefore, these authors postulated that a specific environmental agent, common to both diseases, has diverse expressions in genetically predisposed individuals. Such a hypothesis is supported by the simultaneous infection of the CNS and the gastrointestinal tract by coronavirus and picornavirus in a murine model of MS (17).

In our 4 patients, we observed some remarkable similarities in the clinical course of MS. In all patients the disease debuted with sensory symptoms at the level of the spinal cord. Moreover, disease course was of the relapsing type at onset and moderate to mild. Only one of the patients reached a persistent EDSS of 6 (need for a walking aid). Also the patients described by Kimura, Kitchin and Purrmann were suffering a moderate to mild disease course (17-19). It is tempting to speculate that this is related to the association with IBD in these patients. There
seems to be no difference in concurrence of CD or UC with the course of MS.

In a recent paper, Buljevac et al. reported an association between stressful life events and exacerbations in relapse remitting multiple sclerosis. In their study stress was associated with doubling of the exacerbation rate over the following four weeks (relative risk 2.2, 95% confidence interval 1.2 to 4.0, p=0.014). An extra risk was induced by infections, which were associated with a threefold increase in the risk of exacerbation (52).

Suffering from an IBD relapse could definitely be interpreted as a stressful life event and we expect an increased rate of MS exacerbation following the IBD relapse in the patients with IBD and MS, but this was not observed in our patients. Interestingly and as mentioned above, we observed that the MS disease course of our patients was even moderate to mild. A possible explanation here could be the treatment of IBD in our patients with glucocorticosteroids in the active phase and of azathioprine to keep the disease in remission also had an influence in the disease course of MS.

REFERENCES


