

# Crohn's disease and multiple sclerosis: a single case report

Buccino G.P., Corrente G.\*, Visintini D.

Istituto di Neurologia, Università di Parma, \* Divisione di Gastroenterologia, Ospedale di Parma

*A case of the association of multiple sclerosis and Crohn's disease in a 47 year old patient is reported.*

*A possible relationship between these two diseases has been widely documented, both sporadically and at a familial level.*

*Albeit in the absence of precise experimental data, it is legitimate to presume that the two diseases share common pathogenetic traits*

**Key Words:** multiple sclerosis — Crohn's disease — incidence — immunological findings.

## Introduction

The present case is an association of multiple sclerosis (MS) and Crohn's disease (CD). MS and chronic inflammatory disease of the intestine are affections for which a multifactorial pathogenesis involving genetic, immunological and environmental factors has long been supposed.

A possible relationship between MS and CD was described in 1982 by Rang et al. [19]. While checking the incidence of breast cancer among women who had been colectomised for ulcerative colitis, the author found a higher prevalence of MS than expected: 10 cases among 2261 patients. The relative risk was about 3 times greater than in the general population.

At least at familial level similar findings were reported in two epidemiological studies of distinct populations in Canada: in both cases, the authors found a greater frequency than expected of these diseases in the first and second degree relatives of patients with MS and CD [11, 21].

Furthermore, a few cases of the coexistence of these two pathologies in the same individual have also been described [6, 17] but, as far as we know, this is the first case to be reported in Italy.

## Case report

This 47 year old female patient was first admitted to our Institute in March 1984. She was apparently suffering from thermic and pain anesthesia in her right leg, together with mild weakness in both legs with left side predominance.

Isoelectrofocusing of cerebro spinal fluid (CSF) demonstrated oligoclonal bands. There was an immediate good response to steroid treatment, and the patient was discharged with the presumed diagnosis of demyelinating pathology.

In January 1988, after a period of relative health with no maintenance therapy, the patient suddenly suffered from a sight reduction, which was more marked in her right eye. Ophthalmological examination revealed right sided optic retrobulbar neuritis and right homonym haemianopsia.

T2-weighted cerebral NMR imaging showed optic radiation and rounded hyperenhanced areas in the right occipital lobe and the left optic tract, interpreted as "demyelinating process".

The clinical evolution, neuroimaging and the first CSF result led to a diagnosis of "definite MS" according to Poser criteria [15], with a clinical course in "remitting relapsing form" according to

McAlpine (1972). In January 1992, the patient underwent a second poussée characterized by nausea, morning vomiting, unsteadiness of gait and horizontal nistagmus: NMR examination revealed further demyelination areas chiefly in peritrigonal locations. This episode was treated with prednisolone 3-4 mg/kg pro die in single administration gradually tapered off over one week.

In July 1992, (and therefore eight years after the onset of MS), the patient was admitted to an emergency surgical ward after 20 days of severe abdominal pain, fever, irregular bowell evacuation and abdominal distension.

Explorative laparotomy revealed fluid in the peritoneal cavity, the distension and thickening of the entire colon, and swollen mesenteric lymphonodes.

Appendectomy and the removal of some lymphonodes revealed aspecific lymphadenitis and chronic inflammation of the appendix. The symptoms did not subside and colonoscopy followed: the result was CD (stage IV) extending up to the transverse colon. The morphological and histobiological features indicated chronic inflammatory bowel disease but, as the pathologist declared such findings acute and not specific for either CD or ulcerative colitis, the patient was taken to the gastroenterological ward for further investigations.

The clinical conclusion was at a severe stage (a CD activity index higher than 250) [1] with no neurological signs of any re-exacerbation of the primary disease.

Repeated stool cultures proved negative for both the common (*Shigella*, *Salmonella*, *Staphylococcus*) and less common bacterial agents (*Clostridium*, *Yersinia*, *Campylobacter*, *Mycobacter*, *Enterococcus*).

Therapy was started with parenteral steroids, antibiotics (piperacilline and metronidazole) and 5ASA per os, as well as with topical treatment (i.e., medicated clyster with steroids and 5ASA). As a consequence, there was a rapid and steady improvement in the clinical situation and the principal biological parameters, and a decrease in the signs of the biohumoral activity of the disease. Six months after the diagnosis of CD, the symptoms are still in remission and the patients is still under maintenance oral therapy of 3 g of 5ASA and 8 mg of methylprednisone pro die.

## Discussion

The etiology of MS and CD are unknown, although these diseases probably have a multifactorial background. They both seem to have the same geographical and racial distribution: they have a higher incidence in regions with a temper-

ate climate with an alleged North-South gradient (in Europe, it is 36.5/100.000 cases for CD and 68/100.000 for MS) and both are infrequent among Arabs and Africans, and frequent among Jews [10, 13, 20].

In terms of sex distribution, both have a higher incidence among females (1.15/1 for CD and 1.5/1 for MS). Although they both affect a wide age range, the highest peak is around the second and third decade of age.

Although these data suggest the possibility that environmental factors play a role in both diseases, nothing is known for sure about the responsible microbiological agents. As possible agents for MS, the scrapie agent and Herpes Simplex, Corona, HTLV1 and measles viruses [7] have all been proposed; for CD, paratuberculosis and clamidia [4, 12] organisms have been considered. The simultaneous infection of the CNS and the digestive tract by corona virus and picorna virus was described in 1983 in a murine model of MS [7].

A number of authors have supposed the presence of genetic predisposing factors for both diseases, and there are studies showing a familial association between chronic diseases of the bowel (especially CD) and MS [11, 21, 19].

It has also been hypothesised that one or more genetic loci may determine increased susceptibility to both pathologies; however, it doesn't seem that these include MHI genes. As a matter of fact, an association between CD and HLA B12 (B44) [6] has been verified, but haplotypes HLA A3, B7 and DR2 are more frequently found in MS patients [22]. In our case, immunogenetic analysis demonstrated HLA DR2 positivity, but HLA B/ was negative.

Further immunological characteristics are shared by both diseases:

- 1) the presence of activated circulating lymphocytes (i.e. increased T helpers and a reduction of T suppressors) [22];
- 2) an increase in circulating IL-2 (often related to inflammatory bowel disease activity) [2];
- 3) an increase in circulating lymphocytes with IL-2 receptors [18];
- 4) an increase in circulating soluble IL-2 receptors [9].

Analogous patterns were observed within the lesion: an increase in T helper activated lymphocytes and the presence of cytochines (particularly gamma IFN).

When used as a pharmacological agent, gamma interferon has proved to be a failure in MS, and even a worsening factor in CD [14].

On the mucous epithelial cells in CD and on the surface of astrocytes in MS, class II histocompatibility antigens have been demonstrated.

Sulfasalazopyrine (SSP), a drug used in both the

acute and chronic stages of CD and ulcerative colitis, has been successfully used to treat experimental allergic encephalomyelitis (EAE) [16], the best animal model for MS, providing both clinical and histological results; on the other hand, a case in which MS developed during long-term treatment with SSP has been reported [5]. All of this has been interpreted as an inhibition of the release of LYC4, a product of arachidonic acid metabolism, which is obviously relevant in the pathogenesis not only of EAE, but also of MS and CD. Experiments *in vitro* also indicate the immunosuppressive action of SSP [3].

### Sommario

*Viene riportato un caso di associazione di sclerosi multipla e morbo di Crohn in una paziente di 47 anni.*

*Una possibile relazione tra queste due malattie è stata ampiamente documentata sia a livello familiare, che sporadico. Pur in assenza di precisi dati sperimentali, è lecito supporre che le due malattie condividano tratti patogenetici comuni.*

### References

- [1] BEST W.R., BECKTEL, J.M., SINGLETON J.W., KERN F.: *Development of a Crohn's disease activity index. National Co-operative Crohn's disease study.* Gastroenterology, 70:439-44, 1976.
- [2] BRYNSKOV J., TVEDE N.: *Plasma interleukin-2 and soluble/shed interleukin-2 receptor in serum of patients with Crohn's disease: effect of ciclosporine.* Gut, 795-799, 1990.
- [3] FUJIWARA M., MITSUI K., ISHIDA J., YAMAMOTO I.: *The effect of salazosulfapyridine on in vitro antibody production in murine spleen cells.* Immunopharmacology, 19:15-21, 1990.
- [4] GITNIK G., COLLINS J., BEAMAN B., BROOKS D., ARTHUR M., IMAEDA T., PALIESCHESKY M.: *Preliminary report of isolation of mycobacteria from patients with Crohn's disease.* Dig. Dis. Sci., 34:925-32, 1989.
- [5] GOLD R., KAPPOS, L., BACKER T.: *Development of Multiple Sclerosis in patients on long-term sulfasalazine.* Lancet, 335:409, 1990.
- [6] KITCHIN L.I., KNOBLER R.L., FRIEDMAN L.S.: *Crohn's disease in a patient with multiple sclerosis.* J. Clin. Gastroenterol., 13:331, 1991.
- [7] KNOBLER R.L., RODRIGUEZ M., LAMPERT P.W., OLDSTROM M.B.: *Virologic models of chronic relapsing demyelinating disease.* Acta Neuropathol. (suppl), 9:31, 1983.
- [8] LINDERBERG E., JARNEROT G.: *The incidence of Crohn's disease is not decreasing in Sweden.* Scand. J. Gastroenterol., 26:495-500, 1991.
- [9] MAHIDA Y.R., GALLAGHER A., KURLAK L., HAWKEY C.J.: *Plasma and tissue interleukin-2 receptor levels in inflammatory bowel disease.* Clin. Exp. Immunol., 82:75-80, 1990.
- [10] MAYBERRY J., MANN R.: *Inflammatory bowel disease in rural sub-saharan Africa: rarity of diagnosis in patients attending mission hospitals.* Digestion, 44:172-76, 1989.
- [11] MINUK J.Y., LEWKONIA R.M.: *Possible familial association of multiple sclerosis and inflammatory bowel disease.* N. Engl. J. Med., 314:586, 1986.
- [12] MOSS M.T., GREEN E.P., TIZARD M.L., MAZIK Z.P., HERMON-TAYLOR J.: *Specific detection of Mycobacterium paratuberculosis by DNA hybridisation with a fragment of the insertion element IS 900.* Gut, 32:395-98, 1991.
- [13] ODES H.S., FRASER D., KRUGLIAC P., FENYVES D., FRASER J.M., SPERBER A.D.: *Inflammatory bowel disease in Bedouin Arabs of southern Israel: rarity of diagnosis and clinical features.* Gut, 32:1024-26, 1991.
- [14] PANITCH H.S., HIRSCH R.L., SCHINDLER J., JOHNSON K.P.: *Treatment of multiple sclerosis with gamma interferon: exacerbations associated with activation of the immune system.* Neurology, 37:1097-1102, 1987.
- [15] POSER C.M., PATY D.Y., SCHEINBERG L., ET AL.: *New diagnostic criteria for multiple sclerosis: guideline for research protocols.* Annals of Neurology, 13:227, 1983.
- [16] PROSIEGEL M., NEU I., VOGL S., HOFFMANN J., WILDFEUER A., RUBENSTROTH-BAUER G.: *Suppression of experimental autoimmune encephalomyelitis by sulfasalazine.* Acta Neurol. Scand., 81:237, 1990.
- [17] PURMANN J., ARENDT G., CLEVELAND S., BORCARD F., FURST W., GEMSA R., BERTRAMS J., HENGELS K.J.: *Association of Crohn's disease and multiple sclerosis.* J. Clin. Gastroenterol., 4:43, 1992.

### Conclusions

Experiment results, as well as clinical evidence of familial or the sporadic association of these diseases (as in the present case), lead us to suppose that both diseases share some common traits which still require better definition. We tend to agree with Purmann's theory that, given different genetical backgrounds, the same environmental agents may determine either MS or CD. Further epidemiological and experimental research would be useful to confirm such a hypothesis and plan common therapeutic strategies.

- [18] RAEDLER A., SHREIBER S., WEERH A.D., BOSS A., PETER S., GRETEN H.: *Assessment of in vitro activated T cells in patients with Crohn's disease*. *Hepatogastroenterology*, 37:67-71, 1990.
- [19] RANG E., BROOKE N.B., TAYLOR H.J.: *Association of ulcerative colitis with multiple sclerosis*. *Lancet*, 2:555, 1982.
- [20] "Epidemiologia della sclerosi multipla" in ROSATI G., GRANIERI A.: *Manuale di neuroepidemiologia*. La Nuova Italia Scientifica 1988.
- [21] SADOVNIK A.D., PATY D.W., YANNAKOULIOS G.: *Concurrence of multiple sclerosis and inflammatory bowel disease*. *N. Engl. J. Med.*, 321:762, 1989.
- [22] WAKSMAN J. (Ed.): *Immunological aspects of multiple sclerosis*. *Res. Immunol.*, 140:175, 1989.

Address reprint requests to: Prof.ssa Daria Visintini, Clinica Neurologica, Via del Quartiere 4 - 43100 Parma, Italia