The association of rheumatoid arthritis with multiple sclerosis: report of 14 cases and discussion of its significance.

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Neurologic symptoms may be observed in rheumatoid arthritis (RA), but involve rarely the central nervous system (CNS). Multiple sclerosis (MS) is the most frequent demyelinating disease and has been associated with various chronic inflammatory diseases, but the association with RA is not frequently described (1). Herein, we report a series of 14 patients with the coexistence of RA and MS which enable us to discuss the possible links between these two conditions.

Between 2001 and 2004, a retrospective study was conducted by the *Club Rhumatismes et Inflammation* (CRI), a subgroup of the *Société Française de Rhumatologie*. All the French rheumatologists belonging to the CRI were informed by letter and by the CRI website (www.cri-net.com) to declare the cases of RA and MS occurring in the same patient. The inclusion criteria were the 1987 ACR criteria for RA (2) and the McDonald criteria for MS (3). A rheumatologist was required for the diagnosis of RA and a neurologist for MS diagnosis. The following variables were analyzed: age at RA and MS onset, the presence of extra-articular disease, the presence of joint space narrowing and/or erosions on hand or foot X rays, the presence of rheumatoid factors (nephelometry), antinuclear antibodies (indirect immunofluorescence) and the treatments given for RA, the disease course of MS (remitting/relapsing or progressive), the neurologic symptoms, the brain and/or spinal cord magnetic resonance imaging (MRI) findings , the cerebrospinal fluid (CSF) analysis, the visual evoked potential (VEP) results and the MS treatments. The patient's outcome was also examined. The exclusion criteria were all the other causes of demyelinating diseases (primary Sjögren's syndrome, systemic lupus erythematosus, sarcoidosis, Behcet disease, Lyme disease, HIV or HTLV1 infection). All these conditions were excluded during the initial evaluation of the neurologic disease by the neurologist. Previous anti-TNFα therapy (etanercept, infliximab or adalimumab) was also an exclusion criteria.

Fourteen patients (12 males, 2 females) were declared by 12 rheumatologists (Table 1). The mean age (± SD; years) at RA and MS diagnosis were 47.1 ± 17.5 and 39.8 ± 10.3, respectively. The mean disease duration (years) at the time of the study was 7.6 ± 8.2 for RA and 14.2 ± 11.1 for MS. Rheumatoid arthritis was diagnosed before MS in 3 cases (delay between the two diseases: 12.3 ± 12.1 years) while MS preceded RA in 10 cases (delay: 12.9 ± 8.3 years) and the two diseases occurred simultaneously in one case. One patient had juvenile chronic arthritis and developed joint deformities and erosions. No patient had sicca syndrome, nodules were observed in 3 cases and one patient had Raynaud phenomenon. X-ray erosions were observed in 11 cases and joint space narrowing in 9 cases. No patients had cervical spine subluxation. Tests for rheumatoid factors were positive in 6/14 cases and

antinuclear antibodies were found in only 4/12 cases. Three of these 4 patients had a labial salivary gland biopsy which did not show sialadenitis and the fourth had negative anti-SSA / SSB antibodies. The treatments they received were mainly methotrexate (11/ 14 cases) while other disease modifying antirheumatic drugs were rarely used (leflunomide in 1 case, gold and tiopronin in another case). Most patients received corticosteroids for their arthritis (8 /14 cases).

In parallel, the neurologic disease was of the relapsing/ remitting type in 6 cases and of the progressive type in 8 cases. Magnetic resonance imaging was performed in all cases but results were not available for 2 patients: brain (and/or spinal cord) signal abnormalities were observed in the white matter in all cases. Oligoclonal bands were found on CSF examination in 9 / 11 cases while 2/ 11 analysis were normal (for 3 cases, the CSF analysis was not available). Finally, VEP showed retrobulbar optic neuritis in 4/6 cases and were normal in the 2 other cases (VEP were not available or not performed for the other patients). Treatments of MS were mainly intravenous methylprednisolone (8/14 cases), immunosuppressive drugs (4/14 cases: cyclophosphamide, azathioprine) and/or β interferon (5/14 cases). One patient died due to MS complications and 2 patients were lost of follow-up. The juvenile chronic arthritis case had a severe disease course with advanced articular damage.

The worldwide prevalence of RA has been estimated to 1% while the frequency of MS is 0.1%. Rheumatoid arthritis and MS can be associated with various autoimmune diseases but the association of the two diseases in the same patient has rarely been reported (4,5). In a case control study, 5 cases of RA were found in 155 MS (1.9%) (6). Another study reported that 15% of French MS patients had a first degree relative with autoimmune disease (including Grave's disease, RA, vitiligo, type 1 diabetes mellitus) (7). All these data suggest that an association may exist between MS and another autoimmune disease. Many lines of evidence indicate that MS is a T cell mediated autoimmune disease similar to RA (1,8) with genetic and environmental factors playing a role in their pathogenesis. Rheumatoid arthritis and MS share many similarities regarding their pathophysiology, etiology, histology and certain viruses like Epstein-Barr virus have been incriminated as possible etiologic factor in both disease (1). Another relevant finding was the existence of T cell reactivity against myelin basic protein, the putative autoantigen in MS, for circulating mononuclear cells from RA patients (8).

The relationships between RA and MS were strengthened by the report of demyelinating cases occurring in the course of RA patients under TNFα antagonists. Indeed, 19 cases were reported, 17 following etanercept administration and 2 following infliximab

administration for inflammatory arthritis (9). TNFα is secreted by microglia and macrophages in the CNS and is thought to play a role in myelin and oligodendrocyte damage. Multiple sclerosis patients with progressive disease have high levels of TNFα in their CSF and TNFα CSF levels correlated with the severity of the disease. However, anti-TNFα therapy in MS patients was unsuccessful and tended to increase MS attacks. The description of neurologic events in RA patients receiving TNFα blockers leads to speculate about the causal relationship between the neurologic signs and this treatment. However, the number of these cases did not exceed what might be expected in the general population (10). Alternatively, it can be hypothesized that RA with high disease activity and/or high TNFα levels could favour white matter neurologic lesions. Still, one hypothesis for explaining these neurologic events under TNFα blockers was a latent neurologic disease unmasked by the treatment or a pre-existing neurologic disease (10).

The coexistence of a neurologic disease with an inflammatory arthritis in the same patient may increase disability, alter quality of life and induce psychological disturbances. However, a central neurologic disease may attenuate a joint disease as observed in patients with hemiplegia, reflecting the CNS control of the inflammatory process. Thus, it is conceivable that MS may decrease joint inflammation by regulating the systemic production of inflammatory mediators. In our series, MS did not seem to have an influence on the clinical course of arthritis and *vice versa*. However, this situation did not prevent joint damage in most cases and thus, despite the neurologic disease, RA probably continue to progress. There are no previous reports of the clinical and radiological outcomes of RA in a patient with MS.

Autoimmunity in MS is well demonstrated and it is reasonable to consider that MS patients are prone to develop other autoimmune diseases. Since a great proportion of our patients had initially MS and then developed RA, the best explanation for these cases is a predisposition in MS patients to develop another autoimmune disease with common etiologic cofactors such as RA. In addition, MS usually begins between 20 and 40 years of age while for RA, the disease generally appears between the fourth and sixth decade. With the observance of demyelinating cases during anti-TNFα treatments, it should be recommended to carefully evaluate RA patients before anti-TNFα administration and to avoid this treatment in those with a pre-existing MS diagnosis or a past history of unexplained central neurologic signs or alternatively, a familial history of MS.

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Table 1: clinical, biological and radiological characteristics of the inflammatory arthritis and neurological symptoms and imaging resonance imaging characteristics of the 14 patients with associated rheumatoid arthritis and multiple sclerosis.
(M: male ; F: female ; RA: rheumatoid arthritis ; MS: multiple sclerosis ; MRI: magnetic resonance imaging ; CSF: cerebrospinal fluid; VEP: visual evoked potentials; MTX: methotrexate: CS: corticosteroids; NSAIDs: non steroidal anti-inflammatory drugs; ND: not determined)

Case	Sex	Age at RA diagnosis	Age at MS diagnosis	RA: extraarticular disease	Erosion / joint space narrowing	Rheumatoid factor	Antinuclear antibodies	RA treatments	MS: clinical symptoms	Disease course	MRI	CSF	VEP	MS treatments
1	F	27	22	-	Yes / Yes	+	ND	MTX	Spastic paraplegia Urine sphincter dysfunction Optic neuritis	Progressive	ND	ND	ND	Methylprednisolone Cyclophosphamide β interferon
2	M	52	46	Nodules	Yes / Yes	+	-	MTX	Optic neuritis	Relapsing remitting	Brain lesions	Oligoclonal IgG bands	Abnormal	methylprednisolone
3	M	50	45	-	Yes / Yes	-	-	Leflunomide, CS	Spastic paraplegia Cerebellar syndrome	Progressive	Brain lesions	Oligoclonal IgG bands	ND	Methylprednisolone β interferon
4	F	47	37	-	No / No	-	-	MTX, CS	Optic neuritis paresthesia	Relapsing remitting	Brain plaques	ND	ND	Methylprednisolone β interferon
5	F	64	31	-	Yes / Yes	+	-	MTX,CS	Spasticity, incontinence	Progressive	Brain plaques	normal	ND	Dexamethasone Azathioprine
6	F	24	27	Nodules	Yes / Yes	+	ND	MTX,CS	Spasticity Paresthesia Cranial nerve involvement	Relapsing remitting	Brain plaques	Oligoclonal IgG bands	Normal	Methylprednisolone β interferon
7	F	69	57	-	Yes / Yes	-	-	MTX, CS	Spasticity incontinence	Progressive	Brain plaques	Oligoclonal Ig bands	ND	azathioprine
8	F	40	48	-	Yes / No	-	-	MTX	Spastic paraplegia Incontinence Optic neuritis	Progressive	Cervical cord and brain plaques	Oligoclonal IgG bands	Abnormal	methylprednisolone
9	F	50	31	Nodules, Raynaud syndrome	Yes / Yes	+	1/800	MTX	Optic neuritis V cranial nerve Cerebellar and vestibular syndromes	Relapsing remitting	ND	Oligoclonal IgG bands	Abnormal	CS
10	F	6	32	-	Yes / Yes	-	1/100	Gold salts, tiopronin and MTX	Paresthesia VII cranial nerve	Relapsing remitting	Spinal cord and brain plaques	Oligoclonal IgG bands	ND	Methylprednisolone β interferon
11	F	67	53	-	No / No	-	-	MTX, CS	Spasticity Cerebellar syndrome incontinence	Progressive	Brain plaques	Oligoclonal IgG bands	ND	CS
12	F	43	43	-	Yes / No	+	1/640	NSAIDs	Optic neuritis paresthesia	Progressive	Brain plaques	Oligoclonal IgG bands	Normal	CS
13	F	58	47	-	No / Yes	-	-	CS	Spasticity Optic neuritis Paresthesia incontinence	Progressive	Brain plaques	ND	ND	CS cyclophosphamide
14	F	52	38	-	Yes / no	-	1/320	MTX, CS	Spastic paraparesia Optic neuritis Cerebellar syndrome Incontinence	Relapsing remitting	Brain plaques	normal	abnormal	Methylprednisolone