LETTERS TO THE EDITOR

Neuropsychological analysis in patients with systemic lupus erythematosus: a case control study

Neuropsychiatric involvement is considered an ominous sign in systemic lupus erythematosus (SLE) and a major cause of death. The most frequent symptoms are psychosis, epileptic seizures, chorea, dementia, stroke, peripheral neuropathy and myositis.¹

Neurocognitive decline, such as, poor performance on tasks of simple attention, visuospatial ability and motor dexterity,² has been reported previously in patients with SLE. Marked cognitive impairment was observed in some patients even when there was no overt evidence of nervous system involvement.³ Mental performance did not appear to be related to disease activity or corticosteroid treatment.^{2,3} Cognitive impairment has been regarded as a possible marker of subclinic neurolupus.

We carried out neuropsychological tests on a group of patients with SLE, without clinical evidence of neuropsychiatric involvement, and compared them with a control group of healthy subjects.

The hospital at Jerez is a referral centre for a population of 350 000. We have 63 patients registered as fulfilling the criteria for SLE established by the American Rheumatological Association.⁴ Twelve had clinical neuropsychiatric involvement. From the remaining patients we randomly selected 20 subjects for a prospective neuropsychological study and another 20 sex matched healthy volunteer subjects as the control group. Both, patients and controls were recruited from the same population. The age and educational levels were similar.

A complete clinical examination, standard blood tests and immunological study were carried out. The disease activity was measured by the SLE-DAI system.⁵

Neuropsychological assessment included: Wechsler Adult Intelligence Scale (WAIS),⁶ Wechsler Memory Scale,⁷ Verbal fluency was evaluated by the Set-test,⁸ and depressive symptoms were assessed by the Hamilton Scale for depression.⁹ The neuropsychologist examiner was unaware of the clinical situation of subjects.

Statistical analysis was performed using a non parametric test (Mann-Whitney U test) for mean comparisons between the two groups.

The table shows the mean (SD) for neuropsychological tests. The average age of patients with SLE was 33.2 (range: 17-63) and that of the controls 36.6 (range: 16-61). There were 19 women in both groups. The mean duration of the disease was 71 months (range 12-240). The mean of disease activity was 8.65 (range: 2-21).

Fourteen patients were receiving treatment with less than 15 mg of prednisone, two with more than 15 mg and four were not treated with corticosteroids.

Mean (SD) scores of neuropsychological tests

	Patients n = 20	Controls n = 20	
WAIS			
Verbal Q	91.2 (13.4)	94.1 (19.9)	NS
Performance Q	95 (13)	96.7 (12.1)	NS
Full Scale Q	92.6 (13.1)	96.2 (15.4)	NS
Logical memory	24.3 (3.2)	25.4 (4.2)	NS
Hamilton scale	10.2 (7.6)	8.9 (7.2)	NS
Set-test	38.2 (2.8)	38.7 (1.7)	NS
Age	33.2 (10.4)	36.6 (12.4)	

Q = quotient
NS = not significant

The differences on neuropsychological tests were not significant according to the Mann-Whitney U test ($p > 0.1$).

We concluded that the patients with SLE without clinical neuropsychiatric involvement have a mental performance similar to healthy subjects. Because of the small sample size the results should be interpreted with caution. However, we did not find gross differences between the two groups.

Observing subtle differences in neuropsychological tests that could be used as a marker of subclinic neurolupus is an interesting proposition. We believe that large randomised studies are needed to resolve this question.

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Acute diffuse muscular pain following initiation of methotrexate therapy

We report two cases of an apparently previously undescribed reaction to low dose oral methotrexate therapy for rheumatoid arthritis. Both cases have been reported to the Committee for the Safety of Medicine.

A 70 year old woman with a 20 year history

of seropositive rheumatoid arthritis but with no significant evidence of disease complications was reviewed in the outpatient department. She had previously been treated for six years with enteric coated sulphasalazine to a maximum dose of 500 mg daily; higher doses had made her non-specifically unwell. In 1992 vague abdominal discomfort had caused her to stop the sulphasalazine but she continued to take diclofenac and coproxamol for pain and stiffness. Due to the presence of active synovitis she was started on methotrexate 5 mg weekly.

After the first dose which she took in the evening she awoke the same night with "severe pain in the whole body" which she felt was distinct from her usual joint pain in that it appeared to be located in her muscles rather than her joints. She was unable to move for seven hours due to the pain and stiffness which she described as "like being held down". She felt non-specifically unwell for a further two days. Having felt that this was probably coincidental she took a further dose the following week but developed identical symptoms which again lasted two days. She has now discontinued methotrexate and not experienced any further similar symptoms. Before starting the methotrexate her plasma viscosity was 1.84 cp (NR 1.5-1.72), haemoglobin 11.1 g/dl and immediately after the adverse reaction the plasma viscosity was 1.68, haemoglobin 12.5 g/dl. No other investigations were performed since at the time the patient did not report on the adverse reaction or that she had stopped the methotrexate.

A 48 year old woman had an 18 month history of seropositive erosive rheumatoid arthritis and bronchiectasis. She had previously been treated with D-penicillamine (discontinued due to proteinuria) and sulphasalazine (discontinued due to diarrhoea). Her other medication included coproxamol, diclofenac, prednisolone 2.5 mg daily, ranitidine, bisacodyl, and salbutamol and beclomethasone inhalers. Due to persistent synovitis she was started on oral methotrexate 5 mg weekly. Three hours after the first dose at 5 pm she felt as if she had "severe flu", with widespread aching throughout her body and neck. The following day she felt unable to move due to weakness and pain. She also developed blistering of the mouth. The symptoms lasted three days and fully resolved. They recurred in identical fashion following two further doses of the methotrexate. Before starting the methotrexate her plasma viscosity was 1.76 cp; following the initial doses it rose to 1.83 cp. The full blood count and differential remained unchanged as did her serum biochemistry; creatinine kinase was normal at 31 IU/l (NR 25-200). Since discontinuing the methotrexate there have been no further similar episodes.

The consistent temporal relationship to the methotrexate dose would seem to make a true association likely. We have, however, been unable to uncover any previous reports of a similar adverse event. Unfortunately, in both cases the episode was not witnessed by a physician, and neither patient was willing to undergo rechallenge with the drug under observation due to the severity of the symptoms. The rapid time course is intriguing, suggesting either an immediate hypersensitivity reaction or a pharmacological effect. The onset of action is compatible with the known rapid absorption

of oral low-dose methotrexate.¹ Since the symptoms could suggest rheumatoid disease activity their recognition is important.

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Methotrexate-related pulmonary complications in patients with rheumatoid arthritis: cluster of five cases in a period of three months

Between 11 March and 25 June 1993, five patients with rheumatoid arthritis (RA) were admitted to our unit for suspected methotrexate (MTX)-related pulmonary pathology (table). None had ever smoked or had a history of pulmonary pathology and chest radiographs obtained before MTX treatment had all been normal. Four of five patients were IgM rheumatoid factor and HLA DR4 positive. MTX treatment, resulting in clinical improvement, had been started less than six months before admission in all cases. Each patient had had concomitant treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and two had received low-dose (<10 mg/day) prednisone therapy. All cases presented fever (<39°C) and malaise two to three weeks before admission. Four patients complained of shortness of breath and non

productive cough. Additional adverse effects ascribed to MTX were present in two patients and consisted of abdominal discomfort with loose stools (patient 5) and slight elevation of transaminases (patient 1). On admission, all patients had elevated temperature and were dyspnoeic and tachypnoeic. Mild hand joint synovitis was present in three patients while two others had no signs of active RA. Bilateral basal rales were noted on admission (patients 2, 3, 4) or shortly thereafter (patients 1, 5). ESR and lactate dehydrogenase levels were elevated whereas white blood cell, lymphocyte counts and liver function tests were normal. Slight eosinophilia was present in three cases (patients 3, 4, 5). Blood gas analysis in ambient air revealed frank hypoxaemia at entry (patients 2, 3, 5) or shortly after admission (patients 1, 4).

Chest radiographs showed bilateral interstitial infiltrates, most marked in the lower fields in all cases, which progressed to a diffuse interstitial and sometimes alveolar pattern within some days. Despite extensive investigations (including repeated cultures, bronchoalveolar lavage (BAL) analysis and serological screening) no infectious agent could be identified. Serological tests were negative except for patient 2, who had IgM antibodies and a twofold increase in haemagglutination inhibition titre against type 3 parainfluenza virus. Compared with normal values,¹ BAL cell analysis (table) showed a high percentage of lymphocytes and neutrophils and a low percentage of macrophages in all cases. In patients 3, 4 and 5, an increase in the total number of cells and in the CD4/CD8 ratio was observed. Furthermore, in three cases (patients 1, 3, 4) the percentage of eosinophils was elevated. Lung biopsies were not performed in view of the poor pulmonary condition of the patients and the risks associated with such procedure. Treatment consisted of MTX discontinuation and intravenous fluids, oxygen

and empirical antibiotic therapy until adequate clinical and radiological improvement appeared. Trimethoprim-sulfamethoxazole (TMP-SMZ) (20 and 100 mg/kg/day respectively) was given to four patients for a mean of five days (range two to 10 days) and three patients received erythromycin (4 g/day) for three, four and five days respectively. Prednisolone-sodium-succinate was administered to three patients at doses of 50 mg/day iv for three days and was gradually tapered off. Because of poor oxygenation and deteriorating pulmonary function, four patients were transferred to the intensive care unit and three required mechanical ventilation. All patients survived and have now been discharged. Patient 2 developed inappropriate ADH secretion and deafness during treatment with TMP-SMZ and erythromycin which recovered after stopping these drugs. No other complications were observed although patient 3 experienced a flare up of the RA some weeks after stopping MTX and treatment with azathioprine was started. Chest radiographs before discharge showed improvement but residual abnormalities were present in all cases.

Excluding the present series, eight additional cases of MTX-related pulmonary pathology have been observed in our department in the past nine years. These consisted of four episodes of MTX-pneumonitis (two in the same patient²) and four pulmonary infections.^{3,4} This yields an average of less than one case of MTX-related pulmonary pathology per year.

In summary, we report five cases of MTX-related pulmonary complications admitted to our centre over a period of three months which contrasts with our previous sporadic observations. At least four of them satisfy the criteria for MTX pneumonitis.^{5,6} In one (number 2) a viral infection may have played a role in the pathology observed.

Besides treatment with NSAIDs,⁵ we would not identify any risk factor for the development of MTX toxicity.^{5,7} Since concomitant treatment with MTX and NSAIDs has been a common practice in our centre for years, this seems an unlikely explanation for the cluster we report. Four of five patients were HLA DR4 positive which might suggest a predisposition for MTX toxicity in these patients. More studies are needed to clarify this aspect. Nevertheless, a cluster might be due to a concurrent unidentified factor or may have presented by chance. Though clinical and radiological assessment are warranted to detect occult lung disease before starting MTX therapy, our data underscore the unpredictability of MTX-related lung pathology. Nevertheless, it is important to maintain a high degree of suspicion when a patient develops pulmonary symptoms during low-dose MTX therapy.

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Patient characteristics and laboratory findings at admission

Patient number	1	2	3	4	5
Sex	Male	Female	Female	Female	Female
Age (years)	78	58	63	68	60
IgM rheumatoid factor	Negative	Positive	Positive	Positive	Positive
Disease duration	5.5 months	7.5 months	16 years	17 years	8 years
MTX therapy					
weekly dose (mg)	7.5	7.5	7.5	7.5	15
duration (months)	5.5	4.5	3	4.5	5.75
cumulative dose (mg)	165	135	90	142.5	257.5
Adjunctive therapy	NSAID	NSAID Prednisone 5 mg/day	NSAID	NSAID Prednisone 7.5 mg/day	NSAID
Admission	11-03-93	18-03-93	13-04-93	02-06-93	25-06-93
Examination					
Temperature (°C)	38.8	39.8	38.2	36.8	38.2
Respiratory rate/min	20	32	20	30	28
Laboratory					
ESR (mm)	37	36	69	65	67
WBC count ($\times 10^9/l$)	7.7	7.3	8.2	7.7	9.2
eosinophils (%)	3	2	5	5	5
LDH (U/ml)	405	688	449	352	367
PaO ₂ (kPa) room air	9.4	6.8	6.8	8.6	6.8
BAL fluid analysis*					
Number cell ($\times 10^6/l$)	0.19	ND	0.43	0.40	0.69
macrophages (%)	30		24	19	21
neutrophils (%)	23		30	25	6
eosinophils (%)	16		7	20	0
lymphocytes (%)	27		39	33	73
CD4	ND		66	66	75
CD8			10	23	19
ratio CD4/CD8			6.6	2.9	4.2

ND: not done.

*BAL analysis, normal (SD) values for non smokers¹:

0.161 (0.07) $\times 10^6$ cells/l, 90.1 (4.7)% macrophages, 1.5 (1.2)% eosinophils, neutrophils, 0.2 (0.4)% 8.1 (3.8)% lymphocytes, 45.5 (10.9)% CD4, 31.2 (8.1)% CD8, 1.53 (0.63) ratio CD4/CD8.

LDH normal value: <330 U/ml.