LETTERS TO THE EDITOR

Hyperprolactinaemia in primary Sjögren's syndrome

Prolactin (PRL) is a neuroendocrine hormone that has important immunoregulatory properties. It is a potent mitogen in Nb2 T lymphoma cell line and stimulates both T-cell mediated and humoral immunity.[1] Recently an association between hyperprolactinaemia and certain rheumatic diseases has been described suggesting that PRL may play a role in the pathogenesis of some autoimmune diseases.[2-4] In addition, PRL seems to be an autocrine factor required for viability and proliferation of B lymphoma cells.[5] Furthermore, it was recently proposed that hyperprolactinaemia observed in oestrogen-treated mice may predispose to development of lymphoma in these animals.[6]

Primary Sjögren's syndrome (P-SS) is a chronic autoimmune disease characterised by exocrine glandular insufficiency secondary to lymphocytic and plasma cell infiltration. The spectrum of the disease extends from an organ specific autoimmune disease to a systemic involvement.[7] Characteristically, patients with Sjögren's syndrome (SS) have an increased risk of developing lymphoma.[8]

To investigate an eventual association between hyperprolactinaemia and P-SS, we studied the basal levels of PRL (Radioimmunoassay, NIDDK reagents) in sera from 11 patients with P-SS. The clinical and laboratory characteristics of the patients and their PRL levels are summarised in table 1. Serum from 11 healthy individuals (6 women and 5 men, mean age 40 years) was obtained as controls. All blood samples were obtained at mid morning (always at the same time) and sera were stored frozen at −70°C until tested. None of the patients or controls were taking medication that could increase serum PRL levels (including oestrogen replacement therapy), or had unusual psychological distress that may be associated with increased levels of PRL. All patients had a normal sized sella turcica, normal visual fields, and normal fundoscopic examinations. However, the presence of a pituitary PRL-secreting microadenoma can not be excluded. None of the patients had chronic renal failure, or hypothyroidism.

Sera from five patients (45·5%) were found to have hyperprolactinaemia (PRL > 20 ng/ml).

Table 2 Basal prolactin levels in 11 patients with primary Sjögren's syndrome (P-SS) and controls

Patients and controls	*Prolactin levels (ng/ml)*		*Hyperprolactinaemia (>20 ng/ml)*	
	n	*Mean level*	*n*	*Mean level*
P-SS	11	25·2* (2·8–75·9)	5	40·6 (24·6–75·9)
Controls	11	10·4 (2·3–19·1)	0	–

*Comparison between P-SS and controls: p = 0·04 (Mann-Whitney test). Values in parentheses are ranges. n: Number of individuals.

None of the normal control subjects had hyperprolactinaemia. The mean (SD) level of PRL in P-SS was significantly higher than in controls [25·2 (20 ng/ml *v* 10·4 (7·2) ng/ml, p = 0·04, by Mann-Whitney test] (table 2). We did not find any correlation between levels of PRL and systemic manifestations or the presence of autoantibody (ANA, anti SS-A, anti SS-B, and rheumatoid factor).

These preliminary data showed the presence of hyperprolactinaemia in a subset of P-SS patients. Although there were more females in the patient group all of them were postmenopausal women (without oestrogen replacement therapy), so that high PRL levels were not influenced by oestrogen. The exact cause of hyperprolactinaemia in this subset of P-SS patients needs further investigation. However, it could be a dysfunction of the neuroendocrine system with an imbalance between increased immunostimulatory PRL and decreased immunosuppressive cortisol as has been described in patients with RA.[9] Another potential source of the hyperprolactinaemia found in these patients is the PRL released by lymphocytes. T and B lymphocytes may produce PRL-like proteins that are biologically active that function as autocrine growth factor for lymphoproliferation.[10] Further studies, including a larger number of patients and serial determinations of the hormone to confirm these observations and to establish the exact role of PRL in P-SS, are needed.

MIGUEL A GUTIÉRREZ
JUAN-MANUEL ANAYA
EVANGELINE SCOPELITIS
GUSTAVO CITERA
LUIS H SILVEIRA
LUIS R ESPINOZA
Department of Medicine
Section of Rheumatology
Louisiana State University
School of Medicine in New Orleans
New Orleans, LA, USA

Correspondence to: Dr Luis R Espinoza, LSU Medical Center, Department of Medicine, Section of Rheumatology, 1542 Tulane Ave, New Orelans, LA 70112, USA.

1 Jara L J, Lavalle C, Fraga A, *et al.* Prolactin, immunoregulation, and autoimmune diseases. *Sem Arthritis Rheum* 1991; **20:** 273–84.
2 Jara L J, Gomez-Sanchez C, Silveira L H, Martinez-Osuna P, Vasey F B, Espinoza L R. Hyperprolactinemia in systemic lupus erythematosus: association with disease activity. *Am J Med Sci* 1992; **303:** 222–6.
3 Jara L J, Silveira L H, Cuellar M L, Pineda C J, Escopelitis E, Espinoza L R. Hyperprolactinemia in Reiter's syndrome. *J Rheumatol* (in press).
4 Chikanza I C, Petrous P, Chrousos G, Kingsley G, Panayi G. Excessive and dysregulated secretion of prolactin in rheumatoid arthritis: immunopathogenetic and therapeutic implications. *Br J Rheumatol* 1993; **32:** 445–8.
5 Braesch-Andersen S, Paulie S, Stamenkovic I. Dopamine-induced lymphoma cell death by inhibition of hormone release. *Scand J Immunol* 1992; **36:** 547–53.
6 Walker S E, McMurray R W, Besch-Williford C L, Keisler D H. Premature death with bladder outlet obstruction and hyperprolactinemia in New Zealand Black × New Zealand White mice treated with ethinyl estradiol and 17 beta-estradiol. *Arthritis Rheum* 1992; **35:** 1387–92.
7 Anaya J M, Gutierrez M, Espinoza L R. Sindrome de Sjögren primario. Manifestaciones clinicas extraglandulares. *Rev Esp Reumatol* 1994; **21:** 3–8.
8 Pariente D, Anaya J M, Combe B, *et al.* Non-Hodgkin's lymphoma associated with primary Sjögren's syndrome. *Eur J Med* 1992; **1:** 337–42.
9 Chikanza I C, Petrou P, Kingsley G, Chrousos G, Panayi G S. Defective hypothalamic response to immune and inflammatory stimuli in patients with rheumatoid arthritis. *Arthritis Rheum* 1992; **35:** 1281–8.
10 Sabharwal P, Glaser R, Lafuse W, *et al.* Prolactin synthesized and secreted by human peripheral blood mononuclear cells: an autocrine growth factor for lymphoproliferation. *Proc Natl Acad Sci USA* 1992; **89:** 7713–6.

Interleukin-6, acute phase reactants and clinical status in ankylosing spondylitis

Interleukin-6 (IL-6) may play a role in the pathogenesis of inflammatory disorders such as rheumatoid arthritis (RA) and other inflammatory arthritides.[1 2] We have previously shown that acute phase reactants (APRs) show only minor changes in ankylosing spondylitis (AS). Specifically, in a series of 43 patients with severe AS the numbers with abnormal results for erythrocyte sedimentation rate (ESR), plasma viscosity (PV) and C-reactive protein (CRP) were only 34, 57 and 64% respectively.[3]

We explored therefore the potential of IL-6, in comparison with APRs, to assess disease activity in AS.

Fifty consecutive patients [37 male, 13 female; mean (SD) current age: 46·6 years (13·12)] with primary AS (that is, no

Table 1 Characteristics and prolactin levels of 11 patients with primary Sjögren's syndrome

Case	*Sex*	*Age (yr)*	*Duration of disease (yr)*	*Systemic manifestations*	*ANA*	*Anti SS-A*	*Anti SS-B*	*Rheumatoid factor*	*ESR (mm/h)*	*Prolactin (ng/ml)*
1	F	60	6	V, M, PNS, L	+	+	+	+	52	34·05
2	F	71	2	–	ND	–	ND	–	60	40·63
3	M	28	1	V, PNS	+	+	+	+	ND	75·90
4	F	50	1	K, V, P	+	+	+	ND	76	15·17
5	F	61	6	–	+	–	–	–	ND	28·15
6	F	58	16	L	+	+	+	+	40	12·99
7	F	55	4	R, L, G	+	–	–	ND	109	18·75
8	F	57	12	–	–	–	ND	+	ND	24·63
9	M	58	4	L, M	+	+	+	–	81	9·15
10	F	49	17	A, R, V	–	+	ND	+	ND	2·80
11	F	32	7	V	–	+	–	+	ND	15·40

Abbreviations: F: Female. M: Male. +: Present. –: Absent. ND: Not done. ANA: Antinuclear antibody. ESR: Erythrocyte sedimentation rate. V: Vasculitis. M: Myositis. PNS: Peripheral neuropathy. L: Interstitial lung disease. K: Proximal tubular acidosis. R: Raynaud. G: Atrophic gastritis. A: Adenopathy.

inflammatory bowel disease, psoriasis or Reiter's syndrome) were studied. [Mean (SD) age at onset: 23·3 years (7·46) and mean (SD) disease duration: 23·0 years (12·78)]. Five (4 female, 1 male) had peripheral joint disease.

Interleukin-6 concentrations were compared with a modified Disease Activity Index (DAI),[4] early morning stiffness (EMS), current age, age at onset, disease duration and the APRs.

To determine IL-6 concentrations, anticoagulated venous blood samples from 50 patients were collected at a tertiary referral centre and centrifuged immediately at 1000 × g for 10 minutes. The plasma was subsequently stored at −20°C until used for the assay. The 'IL-6 IRMA' (immunoradiometric assay) kit was used for determining IL-6 concentrations. (Control values <6 pg/ml, supplied by Medgenix Diagnostics, Brussels, Belgium).

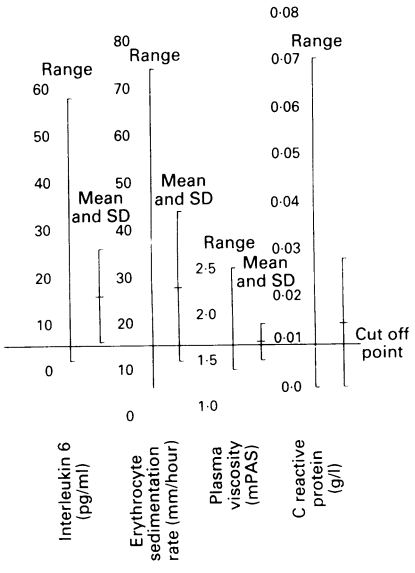
PV (normal 1·50–1·72 mPAS) and ESR (Westergren; normal <15 mm/hour) were determined as were CRP levels by enzyme-linked immuno-absorbent assay (normal <0·01 g/l). Statistical assessments were carried out using Chi-squared or Pearson product-moment correlations.

Forty three of 50 patients (86%) had IL-6 concentrations >6 pg/ml. This involved 84% of the males, all females and all patients with peripheral joint involvement; whereas the number with abnormal ESR, PV and CRP results were 57, 44, 40% respectively (figure). As shown, the mean and 1 SD figures are only above the normal cut off point for IL-6.

When the DAI of 43 patients was analysed it was found that six had low, 28 moderate and nine high disease activity. (DAI: <14 = low, 14–23 = moderate, 24–32 = high). The mean IL-6 values for each group were 13·2, 16·0 and 17·6 respectively. Correlations of the DAI with IL-6, the APRs, age (current and at onset) and duration of disease were all non significant.

Correlations between IL-6 and the APRs, age (current and at onset) plus disease and morning stiffness duration were all non significant. EMS correlated with ESR only ($p = 0·02$).

One patient developed uveitis while being treated as an inpatient. The levels of IL-6 did not alter significantly before or after the flare up (51·7 and 43·9 pg/ml respectively). There were no clinical correlates found for those with high levels of IL-6 compared with those with low levels.



Values for IL-6, ESR, PV and CRP with distribution of results, mean and one standard deviation. Horizontal bar relates to normal cut off values.

Increased serum concentrations of IL-6 have been described in patients with inflammatory disorders such as RA, Crohn's disease[5] and other conditions including major surgery,[6] severe burns[7] and bacterial infections.[8] IL-6 is said to be the major cytokine responsible for APR production by the liver.[9]

Our data revealed that circulating concentrations of IL-6 were increased in the majority (86%) of patients with AS. By contrast abnormal values of ESR, PV and CRP were found in only 57, 44 and 40% respectively. Clearly, IL-6 is a more sensitive 'marker' for AS than the APRs. However, there was no correlation between IL-6 and any of the clinical variables. There was no relationship between IL-6 and the APRs.

This was a cross-sectional study to assess the levels of IL-6 in patients with AS with reference to a previously defined 'normal' level in an unmatched control population. As this study has not produced any biological explanation for the results further studies are required. It would be useful to know how IL-6 varies over time, with treatment and during flares in the disease.

There appears to be at least one laboratory variable that is raised in the clear majority of patients with AS in contrast to ESR, PV or CRP.

We thank the Arthritis and Rheumatism Council for Great Britain, the National Ankylosing Spondylitis Society, the Coates Trust and the Pilkington Trust for their financial support; also Jean Wright and Trish Myers for their secretarial assistance.

Z N TUTUNCU
A BILGIE
L G KENNEDY
A CALIN
Royal National Hospital for Rheumatic Diseases Bath

Correspondence to Dr Andrei Calin, Royal National Hospital for Rheumatic Diseases, Upper Borough Walls, Bath BA1 1RL, United Kingdom

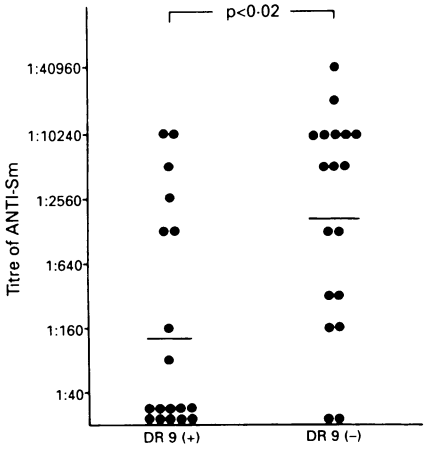
1 Houssieu F A, Devogelaer J P, van Damme J, Deuxchaisnes C, van Snick J. Interleukin-6 in synovial fluid and serum of patients with rheumatoid arthritis and other inflammatory arthritides. *Arth Rheum* 1988; **31:** 784–8.
2 Sawada T, Hirohata S, Inoue T, Ho K. Correlation between rheumatoid factor and IL-6 activity in synovial fluids from patients with rheumatoid arthritis. *Clin Expt Rheum* 1991; **9:** 363–8.
3 Will R, Magaro L, Elswood J, Calin A. Ankylosing spondylitis (AS) and acute phase reactants (APRs). The elusive relationship. *Brit J Rheum* 1989; **26** (S2): 11.
4 Kennedy L G, Edmunds L, Calin A. The natural history of ankylosing spondylitis. Does it burn out? *J Rheumatol* 1993; **4:** 688–92.
5 Gross V, Andus T, Caesar I, Roth M, Scholmerich J. Evidence for continuous stimulation of interleukin-6 production in Crohn's disease. *Gastroent* 1992; **102:** 514–9.
6 Nishimoto N, Yoshizaki K, Tagoh H, *et al.* Elevation of serum interleukin-6 prior to acute phase proteins on the inflammation by surgical operation. *Clin Immunol Immunopathol* 1989; **50:** 399–401.
7 Nijsten M W, de Groot E R, Ten Duis H J, Klesen H J, Hack C E, Aarden L A. Serum levels of interleukin-6 and acute phase responses (letter). *Lancet* 1987; **2:** 921.
8 Waage A, Brandtzaeg P, Halstensen A, Kierulf P, Espevik T. The complex pattern of cytokines in serum from patients with meningococcal septic shock. Association between interleukin-6, interleukin 1 and fatal outcome. *J Exp Med* 1989; **169:** 333–8.
9 Koj A. Definition and classification of acute phase proteins. In: Gordon A H, Koj A, eds. *The acute phase response to injury and infection.* Amsterdam: Elsevier, 1985: 139–232.

HLA antigens in Japanese patients with high titre anti-ribonucleoprotein antibodies

Antibodies to nuclear ribonucleoprotein (nRNP) have been proposed as characteristic of a distinct autoimmune disease, mixed connective tissue disease (MCTD).[1] Previous reports have shown some correlations between genetic factors and MCTD in white groups.[2] However, studies on HLA antigens in Japanese patients with MCTD remain controversial.[3,4] We studied 36 Japanese patients who had anti-nRNP antibodies at high titres to find an association between HLA antigens and autoantibody production.

Thirty six unrelated Japanese patients who had anti-nRNP antibodies at high titres (≥1:10240) were studied. All were women and their mean (SD) age was 37·9 (11·8) years. Thirty two patients fulfilled the criteria for systemic lupus erythematosus (SLE)[5] and the other four were diagnosed as having MCTD according to the disease criteria by Kasukawa *et al.*[6] Twenty four patients had anti-Sm antibodies and twelve did not. All had been suffering from Raynaud's phenomenon. The patients were divided into two groups, one with anti-Sm antibodies (group A, n = 24) and the other without anti-Sm (group B, n = 12). The mean age, the mean duration of the disease and the mean titre of anti-nRNP were not statistically different between the two groups (data not shown). Titres of anti-nRNP and anti-Sm antibodies were detected by passive haemagglutinin test. HLA-A, B, C and DR typing was performed by using standard lymphomicrocytotoxicity method. Chi-square method was used for statistical analysis and the p value was corrected for the number of antigens tested (pc).

Frequencies of HLA-A, B, C and DR antigens in 36 patients and 105 healthy controls are shown in the table. There were no apparent differences between the patient group and healthy controls. Although there were no significant differences between group A and controls, a strong association with DR9 was observed in group B compared with normal controls (83·3% *v* 32·7%, pc < 0·05).



Anti-Sm antibodies in patients with or without HLA-DR9.