Primary Sjögren’s syndrome and aplastic anaemia

Primary Sjögren’s syndrome (SS) is an autoimmune disease characterised by the presence of xerostomia and xerophthalmia without evidence of another systemic autoimmune disease. It has a wide clinical spectrum, extending from exocrinopathy to systemic autoimmune disease and to B cell lymphoma. The association of SS with aplastic anaemia (AA) has rarely been reported and only in patients with lymphoma. We report here an exceptional case of primary SS and severe AA without lymphoma who had cytogenetic and immunological abnormalities, which might give clues to the pathogenesis of AA.

A 28 year old white man was referred in February 1990 for lymphadenopathies and pancytopenia. He complained of xerostomia and ocular burning. Xerostomia was confirmed by a whole saliva flow rate test (right eye 2 mm, left eye 1 mm after 10 min) and a punctate keratitis on slit lamp examination (eye 2 mm, left eye 1 mm after 10 min) and a corneal burn. Xerophthalmia was confirmed by a Ham test, sucrose lysis test, serological tests for HIV, HTLV1, EBV, CMV, and type B and type C hepatitis were negative, serum β2 globulin was normal. Lymph node biopsy showed no adenopathies, or features of idiopathic AA.

The patient was cold and only complained of fatigue. An antilymphocyte globulin (Merieux, Lyon, France; 20 mg/kg/d) with objective improvement was performed. The detection of granulocyte type auto-antibody with the immunofluorescence test. BR Haematol 1978;39:339-43.

However, antilymphocyte globulin, which is present in our patient has not been described in patients with Fanconi anaemia.

The concentration of γ-δ TCR+ cells in our patient was higher than those previously reported in SS. The cultured γ-δ TCR+ lymphocytes expressed a cytotonic function in vitro. This suggests a possible involvement of γ-δ TCR+ cells in the pathogenesis of AA.

The strong correlation between SS and HLA B8 DR3 suggests that genetic factors may play a part in the development of some subgroups of SS. The translocation t(14;20) (q24;p13), present in our patient has not been described before in SS. Interestingly, 1q24 and 2p12-13 are two hypereosinophilic loci that are common among patients with Fanconi anaemia. The gene for transforming growth factor β has also been located in 1q24-25 and this gene is a haematopoietic-suppressor lymphoblast. So, the presence of cytogenetic abnormalities in 1q24 in our patient as well as patients with Fanconi anaemia might lead to an abnormal expression of transforming growth factor β and hence to the suppression of haematopoiesis.

In conclusion, this uncommon finding suggests that an underlying primary SS can be found in the setting of idiopathic AA. Moreover, a high concentration of γ-δ TCR+ cells as well as genetic abnormalities in 1q24 might have contributed to the occurrence of AA.

Fibromyalgia and carpal tunnel syndrome

Recently, Cinimino et al. reported an epidemiological survey on the prevalence of carpal tunnel syndrome (CTS) in patients with fibromyalgia syndrome (FM). These authors found that 9.7% of 93 patients studied in which we reported an association between fibromyalgia and carpal tunnel syndrome. In conclusion, this uncommon finding suggests that an underlying primary SS can be found in the setting of idiopathic AA. Moreover, a high concentration of γ-δ TCR+ cells as well as genetic abnormalities in 1q24 might have contributed to the occurrence of AA.

This study has been supported in part by a grant from Schering AG (Lyis-Iannoni, France).

MATTERS ARISING
they suggest that this 16% means that underlying mechanisms may be common for CTS and FM.

We cannot agree with this suggestion. Our study was not controlled, but no statistically significant differences could be appreciated in the CTS group compared to FM. In our series, 29 of 191 (15.1%) women with FM had CTS in their series despite mean duration of CTS symptoms of 8.1 years (range 6 months to 15 years) while only 23 of 340 (6.7%) women with CTS did not have a previous diagnosis of CTS in the series of de Krom et al.

Both studies are probably biased. In our study, patients with FM and CTS would complain about more severe symptoms and were referred to a rheumatology unit, and thus patients with both CTS and FM would be over-represented in this sample. As pain and paresthesia in the hands are common complaints in patients with FM, CTS was overlooked before rheumatological consultation. Recently, we have carried out studies that may highlight these points: firstly, we have observed that patients referred for rheumatological consultation often have multiple diagnosis at discharge (38%) that explain the musculoskeletal symptoms of the patient. Patients with both CTS and FM had never had a diagnostic suspicion of both diseases previous to rheumatological consultation. In another study of the clinical characteristics of 173 patients with idiopathic CTS (diagnosis was based on neurophysiological studies in all cases), CTS was commonly bilateral and severe, and most patients had been referred with a diagnosis of ‘arthritis’. Again, the prevalence of FM and CTS was high (15%) and patients with FM had significantly more severe CTS than patients without FM. Presence of associated musculoskeletal conditions in patients with CTS or bilateral CTS involvement seem to act as confounding symptoms for correct diagnosis before rheumatological consultation.

In the study of Cimmino et al., 2440 of 4456 of the subjects returned the questionnaire, 182 of 2440 (7.2%) met criteria for clinical examination, and 93 of 182 (51.1%) agreed to be visited. One would expect that patients with both conditions would be more likely to answer the questionnaire and accept consultation.

In conclusion, at the present time, it cannot be stated that CTS is more frequent in patients with FM than in the general population, and common pathogenic mechanisms should not be proposed. Nevertheless, it is clear that CTS is often overlooked or misdiagnosed in patients showing atypical symptoms, such as bilateral, severe CTS, or associated FM before rheumatological consultation. In addition, we feel that rheumatologists should be alert to this possibility of associated CTS and FM, which is probably more frequent in patients referred to rheumatology units than the 2.4% previously reported in a retrospective series.9

**Authors’ reply**

Perez-Ruiz and colleagues raise several interesting points on the relation between fibromyalgia (FM) and carpel tunnel syndrome (CTS). The first point is that in their original paper9 no significant difference in the prevalence of CTS was found between Spanish women with FM (15.1%) and a general population of Dutch women (10.2%).9 However, we feel that comparing populations from different geographical areas may be misleading because environmental and social differences may modulate perception of pain. In fact, data from the US 1988 National Health Interview Survey report a prevalence of self diagnosed CTS of 1.55%.9 To verify the null hypothesis of no association between CTS and FM, a well conducted epidemiological study should be performed in the general population of a single geographical area.

Our previous study was not specifically devised to consider this point. It acknowledged that the insufficient response to the questionnaire could have biased the results toward an over-representation of the association between CTS and FM because the questionnaires were used to identify patients with rheumatic arthritis. We were surprised to find that a considerable proportion of the patients who completed positively to this questionnaire were in fact affected by a combination of FM and CTS.9 Also Perez-Ruiz et al noted that patients attending a rheumatology clinic occasionally show multiple manifestations mimicking inflammatory conditions. In addition, in another abstract, Perez-Ruiz et al report that 19% of patients with CTS have FM and that CTS is more severe in this subgroup. This finding would further support the notion of a common pathogenetic link between the two conditions.

Finally, we agree with Perez-Ruiz et al that patients with FM commonly report paresthesia and pain in their hands. In our experience, FM patients not only often describe paresthesia and pain in the area innervated by the median nerve but also present pain and numbness elicited by specific maneuvers.

However, results of the available diagnostic studies are often negative in FM. A possible explanation is that the median nerve may be involved in FM in a milder degree than in classic CTS. In this setting, electrodiagnostic tests may show a poor sensitivity.

These similarities between FM and CTS give the impression of an association of these conditions. To elucidate whether FM and CTS are really associated, we are presently comparing the electrodiagnostic findings as well as the appearance of the median nerve and the carpal tunnel syndrome in patients with pure CTS or with the presumptive association FM-CTS.

**Measurement of IgA-a-antitrypsin complex in rheumatoid arthritis: A question of specificity?**

We feel we should comment on a recent article by Iwana et al on the clinical value of measuring circulating IgA-a-antitrypsin (IgA-AT) complex concentrations in patients with rheumatoid arthritis (RA) using a prototype ELISA kit. We are concerned about the specificity of the monoclonal antibody used as the capture reagent on the ELISA plates. The authors say that the antibody recognises specific epitopes on the IgA-AT complex. However no direct proof of this is provided here or in previous reports where this particular antibody has been used.10 Recently, in response to another study using this assay we provided data to show that the antibody recognises the complement regulatory protein, factor H.11 We have shown that replacing the ‘complex specific’ antibody with other monoclonal antibodies to factor H (OX23 and OX24) in the ELISA essentially makes no difference to measurement of ‘complex’ values. We have also shown that the ‘IgA-AT’ antibody recognises a different epitope on factor H to that recognised by OX23 and OX24, and feel that it would be surprising if monoclonals directed against three different regions of factor H all showed cross reactivity with IgA-AT.12

Our studies pose the question as to what is actually being measured in the IgA-AT ELISA. The specificity of the complex antibody for factor H might suggest that some form of factor H-IgA complex is being measured. However, a crucial factor in the use of this particular ELISA is the lack of any blocking step (for example, with bovine
author's reply

I thank Dr Azria for pointing out that nasal calcitonin is not licensed in Japan. In addition he is probably correct in stating that nasal calcitonin has few side effects and is acceptable, although this probably reflects lower bioavailability and potentially limited habituation potential, and tachyphylaxis.

Randy M. Davis, MD, PhD


Author's reply

I would like the opportunity to correct, or possibly update, a number of the facts concerning calcitonin contained in Dr Patel's comprehensive review article on drug treatments for osteoporosis.

He states that nasal preparations of calcitonin are licensed for use in osteoporosis in 'some European countries and Japan', whereas in fact the nasal spray formulation of salmon calcitonin developed at Sandoz (now Novartis) is currently approved in more than 70 countries worldwide, including the USA and almost all the countries of Europe, Japan, on the other hand, has not yet granted marketing approval.

Randy M. Davis, MD, PhD

paracetamol or paracetamol/codeine mixtures in the first instance, before consideration of salmon calcitonin. This, in my opinion would be good medical practice, particularly because salmon calcitonin would have to be given by a parenteral route. On the issue of cost, physicians will have to judge the suitability of drugs for osteoporosis depending on their interpretation of efficacy and local price for the individual compounds.

Intra-articular hyaluronan treatment for osteoarthritis

We wish to comment on the article by Stefan Lohmander in which the results of a placebo controlled study with intra-articular hyaluronan in osteoarthritis of the knee were presented.1 It was suggested that aged patients with a high disease severity might be the best ‘responders’ to such a treatment. We felt that it was worthwhile to reanalyse the data of the patients of our German multicentre study with hyaluronan2 to see whether this somewhat unexpected but clinically extremely important hypothesis could be supported. The results of our subgroup analysis clearly seem to indicate again that the patient sample over the age of 60 years and with a high baseline score of >10 Lequesne points is the most likely subgroup to benefit from the treatment (table 1).

Stratified analyses of other methodologically comparable studies or preplanned trials in severe osteoarthritis could contribute to a validated identification of such patients who will probably respond best to an intra-articular treatment with hyaluronan in osteoarthritis of the knee.

<table>
<thead>
<tr>
<th>Evaluation time</th>
<th>All patients (40–75 years, ISK baseline 2.0–18.5)</th>
<th>Subgroup (&gt;60 years, ISK baseline &gt;10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Verum (n=95) Control (n=100) Intergroup difference</td>
<td>Verum (n=28) Control (n=26) Intergroup difference</td>
</tr>
<tr>
<td>1 week after last injection</td>
<td>3.5 2.6 0.9</td>
<td>4.6 3.2 1.4</td>
</tr>
<tr>
<td>Follow up after 1 month</td>
<td>3.8 2.7 1.1</td>
<td>5.7 3.3 2.4</td>
</tr>
<tr>
<td>Follow up after 2 months</td>
<td>4.4 2.8 1.6</td>
<td>6.5 3.6 2.9</td>
</tr>
</tbody>
</table>


Measurement of IgA-α₁-antitrypsin complex in rheumatoid arthritis: A question of specificity?

D L MATTEY, N B NIXON, P T DAWES, L J SCOTT and G I RUSSELL

doi: 10.1136/ard.56.7.439

Updated information and services can be found at:
http://ard.bmj.com/content/56/7/439

These include:

References
This article cites 11 articles, 4 of which you can access for free at:
http://ard.bmj.com/content/56/7/439#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/