No significant sex differences in temporal arteritis.

Eric Liozon, Anne-Laure Fauchais, Veronique Loustaud and Elisabeth Vidal

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No Significant Sex Differences in Temporal Arteritis

To the Editor:

In recent issues of The Journal, Narvaez, et al2 and Nir-Paz, et al6 reported their experience on sex-specific differences in giant cell arteritis (GCA). Narvaez, et al found that among 163 patients with GCA, including 73 with temporal arteritis (TA), the presence of constitutional symptoms was significantly more frequent in women than in men. Women also had a more protracted inflammatory response on laboratory measures. Nir-Paz, et al evaluated 88 patients with either isolated polymyalgia rheumatica (PMR) or TA and found that men and women with GCA differ on their history, presentation, and laboratory findings. Notably, the finding that men are more prone than women to develop irreversible visual ischemia led these investigators to recommend a more aggressive treatment approach to male patients.

These important results compelled us to reexamine the relationship between sex and clinical presentation and prognosis in a large series of patients with TA. Our results, briefly presented below, do not support the view of major sex-related differences in the presenting features of TA, and do not indicate that TA is a more severe disease in men.

Since 1976, we diagnosed and followed 234 patients with TA (190 biopsy-proven, 65 with associated PMR). Diagnosis was according to current criteria. Data were collected prospectively using a comprehensive 174-item questionnaire. Eighty-one patients were men, with a sex ratio of 0.52. All patients were treated according to an established protocol and 215 patients were followed regularly (mean 11 outpatient visits and hospital admissions per patient) for a mean period of 44.6 ± 37.9 months. In addition, 30 patients initially received disulone as part of the therapeutic protocol. Men received disulone more often than women (19.2% vs 11.3%), but the difference was not relevant statistically.

The results of a comparative study of clinical, laboratory, and pathologic features in men and women with TA are shown in Table 1. Men were slightly younger than women. The only sex-related differences in the frequency of disease manifestations were a lower prevalence of rheumatic symptoms and occipitalgia, and a trend toward a higher prevalence of scapular tenderness in men. Permanent visual loss occurred less often in men (8.6%) than in women (14.4%; nonsignificant). The only significant difference in laboratory values was a lower hemoglobin level in women, a self-evident finding. Finally, similar percentages of a positive temporal artery biopsy result were observed in men and women.

A comparative study of comorbid conditions, treatment, outcome, and prognosis in men and women with TA is given in Table 2. Male and female patients did not differ by medical history, the starting prednisone dose, the mean decrement in prednisone dose at 3, 6 and 12 months, mean number of disease relapses, or mean number and type of serious treatment-related side effects. An equal proportion of men and women recovered from TA or died during treatment, and the mean duration of treatment in 110 patients who recovered from TA was not influenced by sex (27.7 ± 14.5 mo in men vs 26.5 ± 12.7 mo in women; NS). Additionally, 10 out of 27 patients whose treatment was continuing at the time of study and had lasted more than 30 months were men.

In this large homogeneous series of patients with TA, we found only subtle sex-related differences in the clinical presentation at diagnosis, in accord with the results of Narvaez, et al. However, we could not confirm on clinical or laboratory grounds the finding by these investigators of a stronger inflammatory response. The reason men have less specific rheumatic manifestations than women is not known to us, but this observation compares with a male to female ratio of 2 to 3 seen in large series of cases of PMR.

More important, the prognosis for visual manifestations did not appear to be worse in male patients. On the contrary, men more often recalled transient visual ischemic symptoms but less frequently developed permanent visual sequelae, compared with women. We have shown previously that the mean platelet count was the only independent predictor for permanent loss of vision in patients with TA, irrespective of the temporal artery biopsy result. We also noted that patients aged 80 years and older had the worst visual prognosis, particularly bilateral irreversible blindness, but that sex had no influence on visual sequelae. Accordingly, 6 studies totaling more than a thousand patients with TA found no differences in sex distribution in patients with and without permanent visual loss.

Finally, beyond the useful considerations on variants of disease presentation, our study, validated by a large sample size and the fact that patients were treated homogeneously and followed closely, emphasizes that men and women with TA possibly share the same prognosis.

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REFERENCES
Drs. Nir-Paz and Chajek-Shaul reply

To the Editor:

Loizou, et al raise once more the intriguing question of sex differences in giant cell arteritis (GCA). This question has been discussed by us and others1-4. In their careful cohort study they show that response to treatment is similar in both men and women, a finding not universally reproduced in other studies5. However, are men and women really alike in their expression of GCA, in both the clinical presentation and response to treatment?

As reported in several studies, the ratio of women to men with GCA is 2. Other differences are noted as well. Women in the Loizou series tend to have more rheumatic symptoms and occipitalgia, while men have scalp tenderness more commonly. Women are also more severely anemic, a feature reported in other studies6. At presentation, we found that men are more prone than women to have jaw claudication, pain upon opening mouth or trismus, maxillary pain, dysphagia, sore throat, hoarseness, lingual discomfort, and dry cough.** Body temperature ≥ 38°C for at least one week and/or weight loss of 5% or more and/or severe asthenia. *** Amaurosis fugax and/or acutely blurred vision and/or diplopia. † At least one test above normal among the following: alkaline phosphatase, gammaglutamyltranspeptidase, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase. †† Number or mean (percentage or range or ± SD). # Chi-square test, Fisher exact test, or Mann-Whitney U test, as needed.

Table 1. Comparative study of clinical, laboratory, and pathologic features in men and women with temporal arteritis.

<table>
<thead>
<tr>
<th>Data</th>
<th>Men, n = 81</th>
<th>Women, n = 153</th>
<th>p**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>74</td>
<td>75.7</td>
<td>0.09</td>
</tr>
<tr>
<td>Associated neoplasm</td>
<td>10 (12.3)</td>
<td>9 (5.9)</td>
<td>0.08</td>
</tr>
<tr>
<td>Acute disease onset</td>
<td>28 (35)</td>
<td>59 (39.1)</td>
<td>0.54</td>
</tr>
<tr>
<td>Delay in diagnosis, days</td>
<td>65.2 ± 80</td>
<td>86 ± 104</td>
<td>0.11</td>
</tr>
<tr>
<td>Abnormal temporal artery</td>
<td>44 (55)</td>
<td>79 (52.3)</td>
<td>0.69</td>
</tr>
<tr>
<td>Rheumatic symptoms</td>
<td>19 (23.8)</td>
<td>59 (38.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Masked (or occult) presentation</td>
<td>8 (10)</td>
<td>15 (9.7)</td>
<td>0.99</td>
</tr>
<tr>
<td>Upper limb artery involvement</td>
<td>11 (13.6)</td>
<td>28 (18.3)</td>
<td>0.37</td>
</tr>
<tr>
<td>Headaches</td>
<td>67 (82.7)</td>
<td>130 (85)</td>
<td>0.62</td>
</tr>
<tr>
<td>Severe</td>
<td>46 (59)</td>
<td>78 (51.3)</td>
<td>0.6</td>
</tr>
<tr>
<td>Occipitalgia</td>
<td>29 (35.8)</td>
<td>79 (53.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Scalp tenderness</td>
<td>48 (60)</td>
<td>59 (45)</td>
<td>0.06</td>
</tr>
<tr>
<td>Ear-throat-mouth symptoms*</td>
<td>41 (51.3)</td>
<td>91 (60.3)</td>
<td>0.18</td>
</tr>
<tr>
<td>Jaw claudication</td>
<td>24 (30)</td>
<td>55 (36.4)</td>
<td>0.38</td>
</tr>
<tr>
<td>Constitutional symptoms**</td>
<td>59 (72.8)</td>
<td>110 (72.8)</td>
<td>0.9</td>
</tr>
<tr>
<td>Transient visual ischemic symptoms***</td>
<td>23 (28.4)</td>
<td>29 (19.1)</td>
<td>0.1</td>
</tr>
<tr>
<td>Permanent visual loss</td>
<td>7 (8.6)</td>
<td>22 (14.3)</td>
<td>0.2</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>3 (3.7)</td>
<td>10 (6.5)</td>
<td>0.5</td>
</tr>
<tr>
<td>Positive temporal artery biopsy</td>
<td>67 (82.7)</td>
<td>123 (80.4)</td>
<td>0.7</td>
</tr>
<tr>
<td>Abnormal liver tests†</td>
<td>35 (49.3)</td>
<td>57 (46.3)</td>
<td>0.69</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate, mm/h</td>
<td>89.4 ± 27</td>
<td>89.5 ± 27</td>
<td>0.9</td>
</tr>
<tr>
<td>C-reactive protein, mg/l</td>
<td>103.7 ± 68</td>
<td>91 ± 56</td>
<td>0.16</td>
</tr>
<tr>
<td>Haptoglobin, mg/l</td>
<td>4798 ± 1545</td>
<td>4677 ± 1976</td>
<td>0.13</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>12.2 ± 2</td>
<td>11.1 ± 1.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Platelet count (GL)</td>
<td>407149 ± 143292</td>
<td>471964 ± 159785</td>
<td>0.13</td>
</tr>
<tr>
<td>Anticardiolipin antibody positivity (IgG)</td>
<td>16 (41)</td>
<td>33 (39.8)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

* Including at least one of the following: jaw claudication, pain upon opening mouth or trismus, maxillary pain, dysphagia, sore throat, hoarseness, lingual discomfort, and dry cough. ** Body temperature ≥ 38°C for at least one week and/or weight loss of 5% or more and/or severe asthenia. *** Amaurosis fugax and/or acutely blurred vision and/or diplopia. † At least one test above normal among the following: alkaline phosphatase, gammaglutamyltranspeptidase, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase. †† Number or mean (percentage or range or ± SD). # Chi-square test, Fisher exact test, or Mann-Whitney U test, as needed.

Different populations may have different patterns of sex differences in GCA, while some variables are measured differently in different studies, suggesting differences that may not exist in fact. As we suggested in our study, in order to observe sex differences a comparison to the general population should be performed as well.

Although Liozon, et al did not find major differences between the sexes, they found some evidence to support our previous study. Further population-based studies on an international basis may shed more light on sex differences in GCA.

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REFERENCES


Dr. Narváez replies

To the Editor:

I read with interest the letter by Liozon, et al presenting their experience on sex-specific differences in temporal arteritis (TA). They compare their results with the 2 main studies that analyzed this question, including our work1,2. The main purpose of our report was to draw attention to the possible importance of sex hormones in TA and polymyalgia rheumatica (PMR). Sex differences are known to exist for many autoimmune diseases. The marked female predominance observed in TA and PMR suggests that sex hormones may play a role in etiology and/or disease expression, although the precise significance of this is still not understood because until recently sex-specific differences in both conditions were not extensively explored. We found modest differences in disease expression between women and men. In the 2 conditions, the inflammatory response seemed to be more severe in women, with greater abnormalities in clinical (constitutional syndrome and fever) and laboratory markers of inflammation. No significant differences in the classical features of TA were observed. Although this has not been clearly elucidated before, 2 other reports on TA from Spanish groups also described a strong inflammatory response in women, supporting our results3-4. Whether this strong inflammatory

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Table 2. Comparative study of response to treatment, treatment-related side effects, recovery from vasculitis, and outcome in men and women with temporal arteries.

<table>
<thead>
<tr>
<th>Data</th>
<th>Results*</th>
<th>p**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting prednisone dose, mg/day</td>
<td>0.76 (0.15)</td>
<td>0.76 (0.16)</td>
</tr>
<tr>
<td>Additional use of diltiazem</td>
<td>14 (19.2)</td>
<td>16 (11.3)</td>
</tr>
<tr>
<td>Mean decrement in prednisone dose at 3 mo, %</td>
<td>56.4 (11.1)</td>
<td>54.6 (11.9)</td>
</tr>
<tr>
<td>Mean decrement in prednisone dose at 6 mo, %</td>
<td>67 (10.8)</td>
<td>67.2 (10.9)</td>
</tr>
<tr>
<td>Mean decrement in prednisone dose at 12 mo, %</td>
<td>82 (10.1)</td>
<td>80.9 (10.8)</td>
</tr>
<tr>
<td>Mean no. of disease flares or relapses per patient</td>
<td>0.69 (0.79)</td>
<td>0.73 (0.85)</td>
</tr>
<tr>
<td>Mean no. of comorbid conditions per patient</td>
<td>1.02 (1.01)</td>
<td>0.99 (0.9)</td>
</tr>
<tr>
<td>Patients with cardiovascular diseases††</td>
<td>30 (42.2)</td>
<td>31 (52.2)</td>
</tr>
<tr>
<td>Mean no. of serious steroid related complications per patient</td>
<td>1.36 (1.37)</td>
<td>1.31 (1.21)</td>
</tr>
<tr>
<td>Vertebral or hip fracture</td>
<td>10 (14.5)</td>
<td>33 (25)</td>
</tr>
<tr>
<td>Hypertension and/or pulmonary embolism</td>
<td>11 (15.9)</td>
<td>19 (14.1)</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>18 (26.1)</td>
<td>37 (27.6)</td>
</tr>
<tr>
<td>Infection</td>
<td>23 (33.3)</td>
<td>35 (25.9)</td>
</tr>
<tr>
<td>Diabetess</td>
<td>14 (20.3)</td>
<td>16 (11.9)</td>
</tr>
<tr>
<td>Gastric or duodenal ulcer</td>
<td>3 (4.3)</td>
<td>5 (3.7)</td>
</tr>
<tr>
<td>Other iatrogenic problems</td>
<td>7 (10.1)</td>
<td>10 (7.4)</td>
</tr>
<tr>
<td>Mean duration of steroid treatment, mo</td>
<td>25.7 (16.3)</td>
<td>23.7 (15.7)</td>
</tr>
<tr>
<td>Length of followup, mo</td>
<td>49.2 (38.1)</td>
<td>44.7 (37.7)</td>
</tr>
<tr>
<td>Recovery from temporal arteritis</td>
<td>42 (57.5)</td>
<td>68 (47.9)</td>
</tr>
<tr>
<td>Duration of treatment in patients who recovered, mo</td>
<td>27.7 (14.6)</td>
<td>26.5 (12.7)</td>
</tr>
<tr>
<td>Death, overall</td>
<td>22 (30.1)</td>
<td>41 (28.9)</td>
</tr>
<tr>
<td>During treatment</td>
<td>14 (19.2)</td>
<td>28 (19.7)</td>
</tr>
</tbody>
</table>

† For each data value, the number of patients available varied from 69 to 73 for men, and 131 to 135 for women. †† Defined by at least one of the following: Hypertension, ischemic heart disease, arrhythmia, stroke. * Number or mean (percentage or range ± SD). ** Chi-square test, Fisher exact test, or Mann-Whitney U test, as needed.
response observed in women implies a lower risk of developing visual loss and other cranial ischemic complications in TA is still controversial, since studies addressing the association between the inflammatory response and the risk of developing irreversible cranial ischemic complications have produced conflicting results. In this regard, we found no differences in the incidence of visual complications by sex. We hypothesized that the more severe inflammatory response observed in women could explain the longer duration of treatment reported in this subgroup of patients in both PMR and TA, regardless of the treatment regimens. Together, these observations indicate that female patients with these conditions can be at particularly high risk for steroid toxicity, a hypothesis that has been demonstrated in PMR.

An additional article addressing sex-specific differences in TA and PMR was published later. In this hospital based study of patients from Israel with either isolated PMR or TA, Dr. Nir-Paz and colleagues found that men and women with both conditions differed in their history, presentation, and laboratory findings. One conclusion of these authors is that ophthalmic involvement, specifically blindness, is more common in men. However, these findings have generated controversy, and recently some investigators have questioned the value of this study for making assumptions about sex-dependent disease characteristics of TA due to its methodological limitations.

Thus the report from Dr. Liozon and colleagues is welcome in order to clarify this issue. Their findings only partially confirm our results, and also reveal subtle sex-related differences in the clinical presentation at diagnosis, without significant differences in the incidence of visual complications by sex. Regarding the laboratory markers of inflammation, they observed lower hemoglobin values in women than in men, without significant sex differences in other measures. Moreover, and contrary to other reports, they did not observe sex differences in the mean duration of treatment or in the incidence of treatment-related side effects. I cannot explain why their results are substantially different in many aspects from previous studies. It seems improbable that these differences can be explained by ethnic differences among different populations, because in another study on TA and PMR from France, Delecourrielle and colleagues found (in contrast to the findings reported by Liozon, et al) that men were more likely to experience visual and other ischemic complications than women, suggesting that “a worse prognosis seems attached to the male sex in TA.” For this reason, the most acceptable hypothesis is that these differences could be related to methodologic differences, including different study designs (prospective versus retrospective studies), selection bias, or the use of specially designed versus standard patient files (the evaluation of clinical findings, when they are mild and do not emerge from a specifically designed study, may have remarkable interobserver variation). In view of these contradictory observations, prospective, multicenter, population based studies will be required to establish universally accepted, clinically relevant conclusions.

While awaiting new data, on the basis of the available studies I feel that sex hormones play a role in the etiology and disease expression of both TA and PMR. This hormonal influence results in a marked female predominance, with a more severe inflammatory response and longer duration of treatment in women. It seems there are not significant sex differences for the risk of visual loss and other cranial ischemic complications; in this clinical aspect, women and men seem to have a similar prognosis.

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labeling on the use of drugs during pregnancy and is in the process of revis-
working to improve the quantity and quality of data available in product
located in the US and Canada, which provide patient counseling and risk
20 comprehensive multidisciplinary Teratogen Information Services (TIS)
resources critically evaluate the literature regarding human and animal
exposed pregnant patients3. In addition, the Organization of Teratology
exposed to their drug in such a registry; the labeling, or package insert, for
misclassification of outcome, including who did the ascertainment
mation on pregnancy outcome without maternal consent. Another bias sur-
rounds the ascertainment of outcome, including who did the ascertainment
and when it was done. The obstetrician or the rheumatologist may be far
removed from an accurate ascertainment of infant health and mothers may
not be the best source to acquire adequate information regarding congeni-
al anomalies. Information on live infant outcomes should be obtained from
the infant’s health care provider. Limiting ascertainment of infant outcome
at birth versus at later time in infancy, e.g., at 3 months, will limit the num-
and type of major malformations reported2. Misclassification of out-
comes may lead to erroneous conclusions.

To proactively encourage the conduct of well designed, scientifically
valid studies in pregnancy, the US Food and Drug Administration (FDA)
recently published a guidance document on establishing pregnancy expo-
registries (http://www.fda.gov/cder/guidance/3626fml.pdf). In these
studies, physicians prospectively enroll their patients after exposure to a
drug during pregnancy but before the outcome of pregnancy is known.
Patients can also self-enroll. These prospective registries offer the opportu-
ity to apply real-world clinical practice data on risk, or lack of risk, to ulti-
mately benefit patient care.

Unfortunately, the authors missed an excellent opportunity to encour-
age rheumatologists to utilize ongoing epidemiologic studies that collect
information on antirheumatic drug exposure during pregnancy. The manu-
factor of Arava6 (leflunomide) is currently enrolling pregnant women
exposed to their drug in such a registry; the labeling, or package insert, for
the product includes a toll-free telephone number for physicians to register
exposed pregnant patients7. In addition, the Organization of Teratology
Information Services (OTIS) is conducting the Rheumatoid Arthritis and
Pregnancy Study, a prospective study to evaluate risks to the embryo or
fetus with the use of rheumatoid arthritis medications in pregnancy. A list of
pregnancy exposure registries in progress for other drugs is available at
www.fda.gov/womens/exposures/default.htm

Current FDA regulations, promulgated in 1979, require prescription
medication labeling to contain a Pregnancy Subsection that includes a
pregnancy letter category (A, B, C, D, or X) that addresses fetal risk of
developmental abnormalities. The FDA recognizes these categories, usu-
ally based only on animal data, can be misleading and that for most prod-
ucts the pregnancy subsection of product labeling provides inadequate
information either for prescribing drugs to pregnant women or for coun-
seling about fetal risks. However, multiple other resources are available to
assist physicians in assessing reproductive toxicities from drug exposures.
For example, the on-line REPRORISK system available from
Micromedex, Inc. contains electronic versions of 4 teratogen information
databases: REPROTEXT, REPROTOX (www.reprotox.org), Shepard’s
Catalog4, and TERIS5. These periodically updated, scientifically reviewed
resources critically evaluate the literature regarding human and animal
pregnancy drug exposures. Other sources of information are the more than
20 comprehensive multidisciplinary Teratogen Information Services (TIS)
located in the US and Canada, which provide patient counseling and risk
assessments regarding exposures during pregnancy (www.otispregnan-
cy.org).

With an eye to the future, the FDA Pregnancy Labeling Task Force is
working to improve the quantity and quality of data available in product
labeling on the use of drugs during pregnancy and is in the process of revis-
regulations that govern pregnancy labeling to delete the pregnancy
category scheme and promote the inclusion of more useful clinical infor-
mation in a narrative format8.

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Dr. Chakravarty, et al, reply

To the Editor:
We read with interest the letter by Dr. Uhl and colleagues in response to our
article about DMARD exposure of pregnant women with rheumatoid
arthritis (RA). We appreciate the interest and discussion raised by our study.
We agree with the points raised by the authors and acknowledge the
limitations inherent in our study. The low response rate is likely, at least in
part, to stem from hesitancy on the part of the physician to disclose infor-
mation about patient outcomes, particularly when they include possible
risks associated with prescribed medications. It is for this reason that we
did not include questions about specific details surrounding pregnancy out-
comes or require detailed review of maternal and infant medical records.
Unfortunately, there is currently a paucity of published information
about pregnancy outcomes with in utero exposure to these DMARD.
Despite over 2 decades of use of methotrexate in the treatment of RA, there
have been less than 25 reported cases of pregnancy outcomes with gesta-
tional exposure to this agent. The aim of our study was to provide clinicians
with additional information about pregnancy outcomes with exposure to
certain DMARD while we await results from prospective studies. Our
intent was to be descriptive rather than to determine accurate estimates of
risks for adverse pregnancy outcomes. We are concerned about and caution
against misinterpretations of the data to suggest relative risk or safety of
any of these DMARD with respect to gestational exposure.
It is clear that prospectively collected data of pregnancy outcomes of
gestational drug exposure are essential to accurately describe and estimate
risks of adverse events. As described by Dr. Uhl, agencies such as the FDA
and OTIS, as well as industry sponsors, have established such scientifical-
ly valid studies. We encourage all providers and patients to enroll in these
registries once pregnancy with exposure to these medications is discovered.
Unfortunately, the same hesitancy on the part of providers to report preg-
nancies to survey questionnaires may still exist when enrolling patients in
pregnancy exposure registries. These include real or perceived legal, ethi-
cal, and confidentiality issues surrounding potential adverse outcomes to
prescribed medications.
There is a need for increased awareness of such registries in order to
enroll the maximum number of exposed pregnancies. We hope that our
study and resulting discussions will encourage increased reporting to vali-
dated pregnancy registries. We applaud the FDA Pregnancy Labeling Task

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“Soft” Neurological Signs in Systemic Lupus Erythematosus

To the Editor:

I recently read the article by Denburg, et al on the relationship of subjective neuropsychiatric complaints to cognitive systemic lupus erythematosus (SLE). The authors conclude rightly that “minor” neuropsychiatric symptoms “may be sufficient to raise suspicion of subclinical nervous system involvement” even when standard objective tests are negative or equivocal.

This view certainly agrees with what I see clinically in my practice. However, the position put forth by the authors should not be limited only to SLE but also to any illness. I am referring in particular to fibromyalgia, where patients often complain of problems with memory, concentration, etc. While it is not practical to obtain brain SPECT scans and other sophisticated objective tests in most fibromyalgia patients, the credibility of such patients should not be challenged since their symptoms, while seeming to be “soft” to us, may be incredibly disturbing to the patient.

THOMAS J. ROMANO, MD, PhD, FACP, 205 North Fifth Street, Martins Ferry, Ohio 43935, USA.

REFERENCE


Dr. Denburg replies

To the Editor:

Dr. Romano writes, ‘The authors conclude that minor neuropsychiatric symptoms “may be sufficient to raise suspicion of subclinical nervous system involvement” even when standard objective tests are negative or equivocal.’

While Dr. Romano’s support is welcome, I would note that the conclusion that he cites, drawn from the article’s Abstract, reads as follows: “minor NP symptoms and, in particular, a small subset of subjective complaints may be sufficient to raise suspicion of subclinical nervous system involvement in the absence of clinically evident NP-SLE.” The intent of the article was to validate the subjective symptoms against objective tests, in this case cognitive tests. Our conclusion was based on data showing that increased subjective complaints were significantly associated with reduced function on these standard objective cognitive tests.

It may be the case that subjective complaints that cannot be validated objectively should be taken seriously in the clinical setting; however, the point of the article was to validate these complaints against objective tests considered to reflect nervous system integrity.

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Validity of the Scleroderma Functional Assessment Questionnaire

To the Editor:

The Scleroderma Functional Assessment Questionnaire (SFAQ) is a relatively new self-report of functional ability designed specifically for persons with scleroderma. The authors state that the Health Assessment Questionnaire (HAQ)

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Table 1. Means and standard deviations for the SFAQ, AHFT, HAQ, HFDS, HAMIS, KFT, and skin scores.

<table>
<thead>
<tr>
<th></th>
<th>dSSc Mean</th>
<th>dSSc SD</th>
<th>ISSc Mean</th>
<th>ISSc SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>SFAQ</td>
<td>7.0</td>
<td>4.5</td>
<td>6.2</td>
<td>6.7</td>
</tr>
<tr>
<td>HFDS (0–66)</td>
<td>24.3</td>
<td>13.8</td>
<td>20.3</td>
<td>21.1</td>
</tr>
<tr>
<td>AHFT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strength total, pounds</td>
<td>122.0</td>
<td>39.0</td>
<td>129.2</td>
<td>43.8</td>
</tr>
<tr>
<td>Dexterity total, s</td>
<td>51.1</td>
<td>11.2</td>
<td>49.8</td>
<td>11.0</td>
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<tr>
<td>Applied dexterity, s</td>
<td>161.5</td>
<td>52.6</td>
<td>145.5</td>
<td>54.4</td>
</tr>
<tr>
<td>Applied strength, mm</td>
<td>4905.1</td>
<td>1184.3</td>
<td>4815.3</td>
<td>1326.3</td>
</tr>
<tr>
<td>HAQ (0–5)</td>
<td>1.1</td>
<td>0.5</td>
<td>1.1</td>
<td>0.75</td>
</tr>
<tr>
<td>KFT (0–42)</td>
<td>17.6</td>
<td>12.4</td>
<td>13.6</td>
<td>9.3</td>
</tr>
<tr>
<td>HAMIS (0–54)</td>
<td>12.2</td>
<td>10.4</td>
<td>6.9</td>
<td>6.8</td>
</tr>
<tr>
<td>Skin score total (0–18)</td>
<td>25.2</td>
<td>15.1</td>
<td>19.8</td>
<td>13.9</td>
</tr>
</tbody>
</table>

AHFT: Arthritis Hand Function Test; HAMIS: Hand Mobility Test in Scleroderma; KFT: Keitel Functional Test; HAQ: Health Assessment Questionnaire; HFDS: Hand Function Disability Scale.

Table 2. Relationships between the SFAQ, performance measures of hand function, and other self-reports.

<table>
<thead>
<tr>
<th></th>
<th>Spearman rs</th>
<th>p</th>
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</thead>
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<tr>
<td>HFDS</td>
<td>0.84</td>
<td>0.0001</td>
</tr>
<tr>
<td>AHFT</td>
<td>–0.50</td>
<td>0.01</td>
</tr>
<tr>
<td>Strength total</td>
<td>0.36</td>
<td>0.05</td>
</tr>
<tr>
<td>Dexterity total</td>
<td>0.35</td>
<td>0.05</td>
</tr>
<tr>
<td>Applied dexterity</td>
<td>–0.62</td>
<td>0.0001</td>
</tr>
<tr>
<td>Applied strength</td>
<td>0.76</td>
<td>0.0001</td>
</tr>
<tr>
<td>HAQ</td>
<td>0.39</td>
<td>0.05</td>
</tr>
<tr>
<td>KFT</td>
<td>0.19</td>
<td>NS</td>
</tr>
<tr>
<td>HAMIS</td>
<td>0.15</td>
<td>NS</td>
</tr>
<tr>
<td>Skin score total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HAQ, KFT, HAMIS, and skin scores. Table 2 shows the SFAQ correlated significantly with the HFDS, AHFT, HAQ, and the KFT.

Our results support the use of a self-report questionnaire, the SFAQ, with persons who have scleroderma. The study provides further support for the concurrent validity of the SFAQ. The SFAQ correlated strongly with the other 2 self-report instruments, as would be expected. As well, 3 of the items on the SFAQ are also on the HAQ and HFDS. Scores also correlated with the AHFT; however, the correlations were weaker. No correlation was found between the SFAQ and skin scores, in agreement with other studies. Yet skin scores have been the traditional outcome used in clinical trials and intervention studies. Interestingly, while the SFAQ correlated with the KFT, the SFAQ did not correlate with the HAMIS. While both of these assessments measure similar joint motions, the KFT consists of 4 items measuring finger flexion, while the HAMIS has only one. However, the HAMIS additionally measures finger extension, and thumb and finger abduction. Perhaps these latter motions are not as important for actual hand function as finger flexion.

In conclusion, clinicians need reliable and valid measures to evaluate the effectiveness of interventions. The SFAQ is simple and quick to administer and has the potential to be useful as an outcome measure of hand function in clinical trials and other intervention studies.

REFERENCES


Lack of Association Between ICAM-1 Gene Polymorphisms and Biopsy-Proven Erythema Nodosum

To the Editor:

Erythema nodosum (EN) is a self-limiting hypersensitivity reaction characterized by multiple and bilateral inflammatory nodules. It may be idiopathic or associated with drugs, several infections, and systemic diseases.

The intercellular adhesion molecule (ICAM-1) is a member of the immunoglobulin superfamily and plays an important role in endothelial cell-leukocyte interactions during inflammation. It contributes to the adhesion and transmigration of most leukocyte types including neutrophils, monocytes, lymphocytes, and natural killer cells through an interaction with ß2 integrins. Expression of ICAM-1 on endothelium is induced by inflammatory mediators, which include lipopolysaccharide and cytokines.

Two coding region polymorphisms have been identified for ICAM-1 — Gly (G) or Arg (R) at codon 241 (exon 4) and Lys (K) or Glu (E) at codon 469 (exon 6). The functional significance of the 469 polymorphism is unknown, although it could potentially lead to alterations in binding and/or costimulator activity of the ICAM-1 molecule. Similarly, the functional influence of the R/G polymorphism at codon 241 remains unclear, although
this region (in exon 4) is in the functionally important domain III of ICAM-1 that contains the binding site for the leukocyte integrin, Mac-1.

ICAM-1 gene polymorphisms have been reported to be important candidate susceptibility factors for multifactorial diseases with an inflammatory component. Given the inflammatory effect of EN, we assessed the implication of ICAM-1 polymorphisms in this condition.

All patients (n = 101, ages 15–78 yrs) in our study were diagnosed with biopsy-proven EN in close collaboration between the rheumatology and dermatology divisions of the Hospital Xeral-Calde in Lugo, Spain. Thirty-six were diagnosed as having idiopathic EN and the remaining 65 as secondary EN (31 of them had EN in the setting of sarcoidosis). Controls (n = 129) were also from Lugo.

DNA from patients and controls was extracted from anticoagulated blood collected in EDTA using a commercial DNA extraction kit (Bioline\texttrademark, London, UK).

Molecular analysis of ICAM-1: as reported\textsuperscript{4}, amino acid polymorphisms, substitution of R for G at codon 241, and substitution of K for E at codon 469 were examined by polymerase chain reaction restriction fragment length polymorphism.

Associations between patient groups and controls and alleles or genotypes of ICAM-1 polymorphisms were estimated using odds ratios (OR) and 95% confidence intervals (CI). Levels of significance were determined by either chi-square or Fisher exact analysis. Statistical significance was defined as p < 0.05. Power calculation was performed for an unmatched case-control study and estimated relative risk using EpiInfo 2000, v. 1.1.2 software.

We found that in the control group, allele and genotype frequencies for ICAM-1 polymorphisms were in Hardy-Weinberg equilibrium; the chi-square data for the observed versus expected genotype for ICAM-1 codon 241 and codon 469 in the control group were 1.9, p = 0.3, and 0.9, p = 0.6, respectively.

No differences between the whole group of patients with biopsy-proven EN and controls were observed for either polymorphism. This was also the result when patients with idiopathic and secondary EN were compared (Table 1). Similarly, no differences between patients with EN associated with sarcoidosis and the remaining group of EN secondary to other etiologies were found (Table 2). A small increase was observed in the frequency of R/G heterozygous for ICAM-1 (241 R/G) polymorphism in patients with EN associated with sarcoidosis compared to the controls (23% versus 13%) (p = 0.2, OR 1.9, 95% CI 0.7–5.1). Given the sample sizes and the allele frequencies of these polymorphisms, we can exclude with 80% certainty a genetic relative risk of 2.7 for ICAM-1 polymorphism at codon 241 and a genetic relative risk of 3.0 at codon 469 for sarcoidosis in Lugo.

ICAM-1 polymorphisms have been investigated in several diseases where diverse genetic and environmental factors are implicated in the development of an inflammatory response. Patients with ulcerative colitis who were antinuclear cytoplasmic antibody-negative had a significantly increased frequency of allele R241 compared with antibody-positive patients\textsuperscript{5}. In patients with multiple sclerosis a significantly higher frequency of the exon 6 homozygote K469 genotype was found compared to controls\textsuperscript{6}. This was independent of the association attributed to HLA-DR2\textsuperscript{7}. In renal transplant recipients allograft failure was associated with R at codon 241, and a more rapid failure of the allograft in the presence of E at codon 469 was also found\textsuperscript{8}. ICAM-1 gene polymorphisms have also been implicated in the pathogenesis of some systemic vasculitides such as in Behçet’s disease and giant cell arteritis\textsuperscript{9,10}.

Our analysis constitutes the first attempt to assess the influence of ICAM-1 polymorphisms in a large series of biopsy-proven EN. Given the sample sizes and the allele frequencies of these polymorphisms, we can exclude a genetic relative risk of those ICAM-1 polymorphisms for EN in Northwest Spain. However, interpretation of these results could to some extent be limited because EN is a very heterogeneous entity.

Table 1. Allele and genotype frequencies of ICAM-1 gene polymorphisms in biopsy-proven erythema nodosum (EN) and controls\textsuperscript{*}.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Controls</th>
<th>EN (total)</th>
<th>Idiopathic</th>
<th>Secondary</th>
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</thead>
<tbody>
<tr>
<td>ICAM-1 (codon 241)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype</td>
<td>n = 129 (%)</td>
<td>n = 101 (%)</td>
<td>n = 36 (%)</td>
<td>n = 65 (%)</td>
</tr>
<tr>
<td>RR</td>
<td>2 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>RG</td>
<td>17 (13)</td>
<td>20 (20)</td>
<td>6 (17)</td>
<td>13 (20)</td>
</tr>
<tr>
<td>GG</td>
<td>110 (85)</td>
<td>81 (80)</td>
<td>30 (83)</td>
<td>52 (80)</td>
</tr>
<tr>
<td>Allele</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>21 (8)</td>
<td>20 (10)</td>
<td>6 (8)</td>
<td>13 (10)</td>
</tr>
<tr>
<td>G</td>
<td>237 (92)</td>
<td>182 (90)</td>
<td>66 (92)</td>
<td>117 (90)</td>
</tr>
<tr>
<td>ICAM-1 (codon 469)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype</td>
<td>n = 117 (%)</td>
<td>n = 98 (%)</td>
<td>n = 34 (%)</td>
<td>n = 64 (%)</td>
</tr>
<tr>
<td>KK</td>
<td>28 (24)</td>
<td>24 (25)</td>
<td>9 (26.5)</td>
<td>15 (23)</td>
</tr>
<tr>
<td>KE</td>
<td>67 (57)</td>
<td>52 (53)</td>
<td>16 (47)</td>
<td>36 (56)</td>
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<tr>
<td>EE</td>
<td>22 (19)</td>
<td>22 (22)</td>
<td>9 (26.5)</td>
<td>13 (20)</td>
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<tr>
<td>Allele</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K</td>
<td>123 (53)</td>
<td>100 (50)</td>
<td>34 (50)</td>
<td>66 (52)</td>
</tr>
<tr>
<td>E</td>
<td>111 (47)</td>
<td>96 (50)</td>
<td>34 (50)</td>
<td>62 (48)</td>
</tr>
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</table>

* No statistically significant differences were observed.

REFERENCES

Table 2. Allele and genotype frequencies for ICAM-1 polymorphisms in patients with EN secondary to sarcoidosis and those due to other etiologies*.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Controls</th>
<th>EN Secondary to Sarcoïdosis</th>
<th>EN Secondary to Other Etiologies</th>
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<tr>
<td>ICAM-1 (codon 241)</td>
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<td>n = 31 (%)</td>
<td>n = 34 (%)</td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>RR</td>
<td>2 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>RG</td>
<td>17 (13)†</td>
<td>7 (23)†</td>
<td>6 (18)</td>
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<tr>
<td>GG</td>
<td>110 (85)</td>
<td>24 (77)</td>
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<td>6 (9)</td>
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<tr>
<td>G</td>
<td>237 (92)</td>
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<td>62 (91)</td>
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<tr>
<td>ICAM-1 (codon 469)</td>
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<td>n = 31 (%)</td>
<td>n = 33 (%)</td>
</tr>
<tr>
<td>Genotype</td>
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<td>28 (24)</td>
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<td>67 (57)</td>
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<td>E</td>
<td>111 (47)</td>
<td>27 (44)</td>
<td>35 (53)</td>
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</table>

* No statistically significant differences were observed. † p = 0.2, OR 1.9, 95% CI 0.7–5.1.

Correction


Signatures for the letter should include the third author, Peter Jacobs, BM, BCh, MD, PhD, The Department of Haematology and Bone Marrow Transplantation Unit, Constantiaberg Medi Clinic, Cape Town, South Africa. We regret the error.