Pro-inflammatory interleukins in the synovial fluid of rheumatoid arthritis associated with joint hypermobility

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Abstract

Background. Joint hypermobility (JH) is frequently seen in rheumatology; in some cases, such as rheumatoid arthritis (RA), it may represent a worsening of disease evolution. The aim of our study was to evaluate the influence of joint hypermobility on RA synovial fluid (SF) inflammation.

Patients and methods. One hundred consecutive adult patients with RA and joint effusion of the knee were examined for the presence of JH. In the SF we evaluated volume, the number of white blood cells (WBC) and the levels of interleukin (IL)-1β, IL-6 and IL-8 and prostaglandin E2 (PGE2).

Results. JH was associated with RA (JH-RA) in 18 patients, all of whom were female. Compared with non-JH RA, all the SF indices found in JH-RA were higher, although significant differences were observed only for volume, IL-8 and PGE2.

Conclusion. In JH-RA, increased joint mobility seems to be associated with a more severe local inflammatory response, which may contribute to the more erosive evolution observed in our patients.

Key words: Joint hypermobility, Rheumatoid arthritis, Cytokines, Prostaglandins, Synovial fluid.

Joint hypermobility (JH) is frequently observed in rheumatology and represents an increase in the mobility of both small and large joints beyond the normal range. This condition exists to a substantial extent in the normal population; most hypermobile people are asymptomatic but some develop the benign joint hypermobility syndrome [1]. This syndrome is defined as the occurrence of musculoskeletal symptoms in hypermobile subjects in the absence of systemic rheumatological disease [2]. The frequency of JH varies according to age, sex and race; it prevails in children, women, Africans, Asians and Arabs [1, 3].

The association between JH and rheumatic manifestations has been confirmed by several authors, being found with increased frequency in extra-articular disorders [4], but also in inflammatory arthropathies, including rheumatoid arthritis (RA) [5–7].

In an attempt to clarify the role of JH in RA, we investigated the possible influence of JH on synovial fluid (SF) inflammation in patients with RA (RA-JH patients) compared with RA patients without JH (non-JH patients).

Patients and methods

We examined 100 consecutive RA patients (ACR criteria [8] aged >18 yr (12 males and 88 females, median age 40 yr, range 19–74), with disease duration less than 2 yr and with joint effusion of the knee. The presence of JH was evaluated according to the criteria of Carter and Wilkinson [9] modified by Beighton et al. [3]. For the purposes of this study, patients were considered hypermobile if their mobility score was greater than or equal to 5.

The score for erosions was obtained by counting the number of erosions in each finger joint and wrist by the same radiologist, who was blinded to clinical findings.

SF was obtained by arthrocentesis of the knee, and was subjected immediately to chemical, physical and microscopic examination, including volume, number of leukocytes (WBC) and the presence of crystals. The remaining part of the sample was centrifugated to remove cells and debris and stored at −70°C for further analysis of interleukin (IL)-1β, IL-6, IL-8 and prostaglandin E2 (PGE2).
Table 1. Main demographic and laboratory findings of patients with JH and non-JH patients

<table>
<thead>
<tr>
<th>Patient group</th>
<th>No. of patients</th>
<th>Age (yr): median (range)</th>
<th>Disease duration (months): median (range)</th>
<th>No. of active joints</th>
<th>ESR (mm/h)</th>
<th>CRP (mg/dl)</th>
<th>No. of X-ray erosions of the hand</th>
</tr>
</thead>
<tbody>
<tr>
<td>JH</td>
<td>18 (18)</td>
<td>35 (19–69)</td>
<td>15 (6–23)</td>
<td>9.5 ± 5.3</td>
<td>40.3 ± 28.2</td>
<td>2.3 ± 1.9</td>
<td>3.5 ± 1.6</td>
</tr>
<tr>
<td>Non-JH</td>
<td>82 (70)</td>
<td>45 (19–74)</td>
<td>14 (6–23)</td>
<td>10.6 ± 4.9</td>
<td>41.4 ± 33.3</td>
<td>3.2 ± 2.8</td>
<td>2.1 ± 0.9</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are mean ± s.d., except for age and disease duration.

Table 2. Main synovial fluid features and levels of interleukins and PGE2 in patients with JH and non-JH patients

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Volume (ml)</th>
<th>WBC (× 10³/µl³)</th>
<th>IL-1β (pg/ml)</th>
<th>IL-6 (pg/ml)</th>
<th>IL-8 (pg/ml)</th>
<th>PGE2 (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JH</td>
<td>41.3 ± 12.2</td>
<td>21.3 ± 18.4</td>
<td>27.3 ± 12.8</td>
<td>1074.2 ± 345.2</td>
<td>876.2 ± 336.0</td>
<td>102.2 ± 24.8</td>
</tr>
<tr>
<td>Non-JH</td>
<td>27.2 ± 11.5</td>
<td>19.2 ± 11.9</td>
<td>22.3 ± 10.2</td>
<td>875.2 ± 234.1</td>
<td>487.3 ± 298.4</td>
<td>67.4 ± 16.3</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.0001</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are mean ± s.d.

Cytokines were determined by ELISA methods (IL-1β, R&D Systems, Minneapolis, MN, USA, limit of detection 0.3 pg/ml; IL-6, Tell Sciences, Needham, MA, USA, limit of detection 7 pg/ml; IL-8, R&D Systems, limit of detection 3 pg/ml). PGE2 was determined by radioimmunoassay using a commercial antisera from Institut Pasteur, Paris, France.

Statistical analysis was performed using Student’s t-test.

Results

JH was identified in 18 patients (18%), all of whom were female, with an average age of 35 yr (range 19–69). Of the 82 non-JH patients, 12 were male and 70 female, with an average age of 45 yr (range 19–74).

No differences were observed between the two groups as regards age, disease duration, number of active joints, erythrocyte sedimentation rate and C-reactive protein concentration, whereas the number of erosions in the hand on X-ray was higher in JH (3.5 ± 1.6) than in non-JH patients (2.1 ± 0.9, P < 0.0001) (Table 1).

Regarding SF, all parameters evaluated (volume, WBC, IL-1β, IL-6, IL-8 and PGE2) were higher in JH than in non-JH patients. However, significant differences were observed only for volume, IL-8 and PGE2, which were higher in JH (41.3 ± 12.2 ml, 876.2 ± 336.0 pg/ml and 102.2 ± 24.8 pg/ml respectively) than in non-JH (27.2 ± 11.5 ml, P < 0.0001; 487.3 ± 298.4 pg/ml, P < 0.0001; 67.4 ± 16.3 pg/ml, P < 0.05, respectively) (Table 2).

No correlation was found between Beighton’s score and the SF parameters.

Discussion

The results of this study show that the percentage of RA patients with JH was not negligible (18%) and was clearly higher than that in the normal population (2–5%) [1, 5–6, 10]. Our data are in keeping with those of Bridges et al. [5], indicating that JH is more prevalent in autoimmune rheumatic diseases, as also suggested by the characteristic features of subluxations and Jaccoud’s syndrome in systemic lupus erythematosus [11].

Concerning the possible influence of JH on joint disease, we observed that some important indices of SF inflammation, such as volume and the levels of IL-8 and PGE2, were higher in JH than in non-JH RA. The reasons for these differences are difficult to explain. It is possible that the laser capsule may allow a larger volume of SF in the JH RA group. However, the higher quantity of SF found in hypermobile patients causes an increase in the intra-articular pressure, which is then exacerbated by joint motion. This may aggravate local inflammation through a hypoxic/reperfusion mechanism, which in turn causes oxidative injury due to intermittent ischaemia [12–13]. Thus, increased levels of radical oxidative stress products may result. The influence of these substances on inflammation has been widely demonstrated and, among the different effects, there is stimulation of various cell types to produce some inflammatory cytokines, including the neutrophil-chemotactic IL-8, which ensures the recruitment of neutrophils to the area of reperfusion injury [13–16].

If we consider the inflammatory process as a reparative response to localized cell death and the release of altered proteins due to hypoxia, the mediators of inflammation described above play an important role in the initiation and maintenance of an inflammatory lesion. The first step is the induction of host adhesion molecules which mediate the capture, rolling, adhesion and transmigration of immunomodulatory cells from circulation. These cells release many substances, such as growth factors and cytokines, which cause a proliferative response of fibroblasts in inflamed tissues, producing substances such as IL-8 and prostaglandins. The latter are involved in the acute regulation of vascular alterations during inflammatory reactions. In detail, PGE2 is important both endogenously and exogenously in the pathology of arthritis, and can modulate the induction of IL-8 by IL-1 in human synovial fibroblasts [17–18]. Thus, it is possible that this type of inflammatory
response influences the outcome of disease in RA. In keeping with this hypothesis is the finding of higher numbers of X-ray erosions in the hands in JH compared with non-JH RA patients.

In conclusion, we believe it is opportune to look for and evaluate the presence of JH in patients with RA, since this condition may represent a worsening of disease evolution, emphasizing both typical articular problems and local inflammation.

References

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