Serum amyloid protein levels in South American children with rheumatoid arthritis: a co-operative study

MORTON A. SCHEINBERG, OSVALDO HUBSCHER, OSVALDO GARCIA MORTEO, AND MERRYL D. BENSON

From the Division of Microbiology–Immunology, Pathology Department, Faculdade de Ciências Médicas da Santa Casa de São Paulo; the Bone and Joint Research Unit, Pavilhão Fernandinho Simonsen, Department of Orthopedics; Centro de Educacion Medica e Investigaciones Clinicas CEMIC, Buenos Aires, Argentina, and the Division of Rheumatology, University of Indiana, Indianapolis, USA

SUMMARY Serum amyloid protein (SAA) levels were determined by radioimmunoassay in 90 children with juvenile rheumatoid arthritis (JRA). Significantly higher levels of SAA were present in children with the polyarticular and systemic forms of the disease. SAA levels correlate with disease activity, increasing during acute exacerbations, decreasing during remission and in patients having prednisone therapy. High serum SAA concentrations in children with JRA did not correlate with the presence of secondary amyloidosis and may be useful as a disease monitor.

There is a difference in the frequency of secondary amyloidosis in juvenile rheumatoid arthritis (JRA) in European countries when compared to the frequency reported in North and South America.\(^1\)\(^-\)\(^5\) A number of factors have been suggested as playing a role in the pathogenesis of secondary amyloidosis. However, none of these factors can by itself account for the difference in the incidence of amyloidosis-associated JRA throughout the world.

During the past 10 years progress has been made in the analysis of the structure and chemical composition of amyloid. Fragments of immunoglobulin have been found to be the major fibril protein in the primary form of amyloid disease. The second type of amyloid protein is a serum protein, SAA, which has the properties of an acute phase reactant. The SAA protein appears to be the precursor of amyloid AA, which is the amyloid protein associated with secondary amyloidosis encountered in patients with chronic inflammatory conditions such as juvenile rheumatoid arthritis. In the present study we have measured the level of serum SAA in South American JRA children with and without amyloidosis and compared it to the levels in patients with JRA from other parts of the world. We have also determined the correlations between SAA levels and the various clinical forms of JRA, disease activity, and the effect of therapy.

Material and methods

The determinations of SAA levels were performed on a group of 90 children who were seen regularly in the arthritis clinics in 2 different countries, namely, Argentina and Brazil. The Argentinian group consisted of 60 children (40 females, and 20 males) with JRA, 4 of them known to have biopsy-proved amyloidosis. The Brazilian group consisted of 30 children (18 females, and 12 males) with JRA who fulfilled previously established diagnostic criteria.\(^6\)

Serum SAA concentrations were determined by radioimmunoassay. Briefly, SAA antisera was raised in rabbits by the injection of isolated protein AA in New Zealand white rabbits by serial injections of AA in complete Freund's adjuvant. Radiolabelling of human amyloid protein AA was performed by iodium utilising Hunter's method.\(^7\) The radiolabelled AA was stored at \(-20^\circ\)C until used. The assay itself was performed by competitive binding as described by Yalow and Berson with small modifications.\(^8\) The method measures the
concentration of serum as AA equivalence in
international units/ml.

Results

In children with JRA the higher levels of SAA were
found in patients with the systemic form of the
disease, with a mean value of 3240 ± 628 U/ml,
followed by the polyarticular group with a mean
value of 2035 ± 321. The oligoarticular group had a
mean SAA level of 411 ± 118, which differed signifi-
cantly from the 2 other forms of the disease
(Table 1). Children with JRA and amyloidosis had
values that were comparable to those observed among
the JRA children without amyloidosis.

When JRA patients were grouped according to the
activity of the disease, SAA levels were significantly
higher in the active group, suggesting that SAA
levels may be a good indicator of disease activity
(Table 2).

To assess the effect of therapy on SAA levels
JRA patients on steroid therapy were compared to
those not receiving the medication. The steroid
treated group had mean SAA levels 1434 ± 275
U/ml, significantly lower than the nonsteroid group
(2699 ± 471) (Table 3).

No correlation could be established between the
Westergren sedimentation rate and serum SAA
levels; there was considerable variation from indi-
vidual to individual.

Table 1  SAA protein levels in South American
JRA children: Course of disease

<table>
<thead>
<tr>
<th>Systemic</th>
<th>Oligoarticular</th>
<th>Polyarticular</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAA protein (U/ml)</td>
<td>3240 ± 628</td>
<td>411 ± 118</td>
</tr>
<tr>
<td>No. of patients</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>SAA protein, normal values</td>
<td>58 ± 5</td>
<td>58 ± 5</td>
</tr>
</tbody>
</table>

1P<0.01 when compared to the systemic and polyarticular forms.

Table 2  SAA protein levels and disease activity

<table>
<thead>
<tr>
<th>Active</th>
<th>Inactive</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>55</td>
</tr>
<tr>
<td>SAA protein (U/ml)</td>
<td>2573 ± 314</td>
</tr>
</tbody>
</table>

1P<0.011 when compared to the inactive form.

Table 3  SAA protein levels and prednisone therapy

<table>
<thead>
<tr>
<th>Nonsteroidal therapy</th>
<th>Prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>60</td>
</tr>
<tr>
<td>SAA protein (U/ml)</td>
<td>2699 ± 471</td>
</tr>
</tbody>
</table>

1P<0.01 when compared to the nonsteroidal group.

Discussion

The present study attempts to correlate serum SAA
levels with the various clinical parameters of JRA.
High concentrations of SAA protein in serum were
found in children with the systemic and polyarticular
forms of the disease, particularly if the condition
was active at the time of removal of the blood. The
activity of the disease in the present study was
estimated on the basis of the elevation of the sedi-
mentation rate, number of active joints, and pres-
ence of fever and/or arthritis.

The mean concentration of SAA protein in
amyloidotic children did not differ from that in non-
amyloidotic children, indicating that SAA values can-
not be used to assess or predict the development of
amyloidosis. This agrees with previous studies.5, 9

It should be noted that the low frequency of amy-
loidosis in this study group may in part reflect the
small number of children with systemic disease,
in whom amyloidosis appears to be a more pre-
valent condition. The lower levels of SAA protein
in children receiving oral steroids correlates with
the well known anti-inflammatory properties of
these agents and the acute phase reactant behaviour
of SAA protein and the previous reported low SAA
levels on JRA patients receiving cytotoxic therapy.9

In conclusion, these studies show that serum SAA
levels in JRA children are not related to the develop-
ment of secondary amyloidosis. We reported
similar findings in experimental studies on mice,
where SAA levels do not correlate with the develop-
ment of casein induced amyloidosis in susceptible
and resistant strains of mice.10–12 Higher SAA levels
are more a reflection of disease activity and the
medication used by the patient. The absence of a
good correlation between SAA and sedimentation
rate suggests, however, that neither of those 2 par-
eters should be used alone to detect disease activity.
The regional differences in the incidence of amy-
loidosis in JRA throughout the world appear not to be
dependent on SAA protein levels but perhaps on
other mechanisms that should receive attention.

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