Serum Aminoterminal Propeptide of Type III Procollagen in Systemic Sclerosis

A Follow-up – Investigations in Subclasses and during Therapy

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Fifty-seven patients with systemic sclerosis were investigated for connective tissue turnover related to type III collagen. Sera from 13 patients with diffuse cutaneous systemic sclerosis and 44 patients with limited cutaneous systemic sclerosis were analysed for aminoterminal propeptide of type III procollagen (PIIINP) by a radioimmunoassay based on human propeptide. Increased levels of PIIINP in serum correlated with skin involvement and the clinical course. All patients with diffuse cutaneous systemic sclerosis had levels above the normal range, and in limited cutaneous systemic sclerosis elevated PIIINP levels seemed to be correlated with rapid progression and extension of lesions. Immunosuppressive drugs, cyclosporin A, and prednisone with or without cyclophosphamide, which were given to patients with rapid disease progression, significantly reduced PIIINP. This was also the case with penicillamine, but to a lesser degree. Our data support the suggestion that immunosuppressive agents are justified in rapidly progressive, life-threatening or disabling disease, when used with the necessary precautions. Serum PIIINP may be utilized as a marker of type III collagen fibrogenesis in systemic sclerosis and be of prognostic value. PIIINP may also be of use in the differential diagnosis between diffuse cutaneous systemic sclerosis and sclerodema.

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Systemic sclerosis (SS), or systemic scleroderma, is characterized by progressive fibrosis of the skin and internal organs (1). In the skin, the accumulation of type I and III collagen (2,3) seems to arise from increased synthesis rather than from decreased degradation (4). SS consists of diffuse cutaneous SS and a limited cutaneous SS (5). The latter may be subdivided into two groups according to skin involvement (6): type I which has only sclerodactyly with no lesions above the wrists, and type II, an acrosclerosis with additional involvement of areas proximal to the wrists.

The radioimmunoassay for serum aminoterminal propeptide of type III procollagen (PIIINP) was first studied in SS by Kriegl et al. in 1986 (7). We published preliminary data on PIIINP in relation to SS and localized scleroderma in 1988 (8). The present paper is a follow-up of this study, after the improved method by Risteli et al. (9) has been used for more than 3 years with all patients with SS consulting our department. We also report on serum PIIINP determinations performed before and during treatment.

PATIENTS AND METHODS

Sera were collected from 57 patients with SS, 13 with diffuse SS, 16 with type II SS, and 28 with type I SS. All patients fulfilled the criteria of the American Rheumatism Association (10). For 26 of the patients, serum PIIINP was determined before therapy or after at least 6 months without treatment. Thirty patients were studied before and after treatment with penicillamine given in dosages from 250 mg to 750 mg per day. Six patients were studied before and after cyclosporin A treatment (1.5 mg/kg to 7 mg/kg) and from nine serum was collected before and after therapy with prednisone (3 patients) or without (6 patients) cyclophosphamide. Cyclosporin A and prednisone/cyclophosphamide treatment was only used in early and very active SS and in SS with pronounced progression.

All patients were studied with respect to serum creatinine, alkaline phosphatase and aspartate aminotransferase. Patients with suspected kidney involvement were studied with creatinine- and chrom EDTA clearance, and in 6 cases a kidney biopsy was performed. A liver biopsy was done in one patient in which laboratory tests and history indicated possible biliary cirrhosis. Other internal manifestations were diagnosed by lung X-ray, lung function tests, echocardiograms, and studies on esophageal motility. Patients with suspected joint involvement had an X-ray of these joints, in general X-ray of the hands.

Serum PIIINP levels were measured by the radioimmunoassay based upon the human propeptide (9), with the kit from Fimoms Diagnostica, Oulunsalo, Finland. The refer-
Fig. 1. Serum PIHNP levels in systemic sclerosis. The patients were subgrouped in diffuse cutaneous systemic sclerosis (diffuse scleroderma) and limited cutaneous systemic sclerosis with no lesions above wrists (type I) and with lesions above wrists (type II). □, patients studied before or at least 6 months after discontinuation of treatment; ●, patients on systemic treatment. A horizontal line indicates upper normal limit.

ence range based upon healthy Finnish blood donors (n = 88) is 1.7–4.2 µg/l. Similar results on healthy Danish controls were 2.1–4.3 µg/l (n = 39, mean ± SD). All sera were stored at −20°C until analysis.

Statistical analyses were performed by the Wilcoxon's test for paired differences and Student's t-test (Fig. 1).

RESULTS

All patients with diffuse SS had PIHNP serum values above the upper reference level. The same applies for 9 of 16 patients with type II SS, and 3 of 28 patients with type I SS (Fig. 1 and Table I). Patients with SS as a whole had higher levels than controls (2p < 0.001), and this also applies to the subgroups with diffuse scleroderma (2p < 0.001) and type II SS (2p < 0.001), but not to patients with type I SS. Pretreatment values were significantly higher than values after treatment with cyclosporin A (2p < 0.05) (Fig. 2) or prednisone with and without cyclophosphamide (2p < 0.05) (Fig. 3). In all cases, pretreatment values were compared with the first posttreatment investigation.

Serial investigations showed that some patients had a later increase in serum PIHNP, generally corresponding to an exacerbation of their disease. During penicillamine treatment there was an initial decrease in PIHNP (2p < 0.05) (Fig. 4).

Four patients had pathological liver tests. One of these was the patient with type II limited SS in which...

Table I. Mean serum PIHNP in systemic sclerosis (SS) subclasses.

<table>
<thead>
<tr>
<th>Patients Type</th>
<th>n</th>
<th>Serum PIHNP µg/l</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>mean ± SD</td>
</tr>
<tr>
<td>DS</td>
<td>13</td>
<td>7.9 ± 3.7</td>
</tr>
<tr>
<td>Type II LSS</td>
<td>16</td>
<td>5.6 ± 1.4</td>
</tr>
<tr>
<td>Type I LSS</td>
<td>28</td>
<td>3.6 ± 0.9</td>
</tr>
<tr>
<td>All SS</td>
<td>57</td>
<td>5.1 ± 2.7</td>
</tr>
<tr>
<td>Controls</td>
<td>39</td>
<td>3.2 ± 0.6</td>
</tr>
</tbody>
</table>

Fig. 2. Serum PIHNP before and following initiation of therapy with cyclosporin A.
of Raynaud’s phenomenon, lung function status or decrease in esophageal motility. Joint involvement was too rare to be evaluated. Only in one patient a rise in PIIINP levels and clinical status suggested increased fibrogenesis of internal organs. This case was the type II SS patient with biliary cirrhosis. Increased serum PIIINP has been found in a number of liver diseases with fibrosis and/or cirrhosis (13,14). Our study indicates that PIIINP may be of use to distinguish between diffuse scleroderma and sclerodema. In sclerodema PIIINP serum levels are normal (Zachariae & Heiekendoff unpublished data).

The mounting evidence that humoral and cell-mediated immune abnormalities play an important role in the pathogenesis of SS, and especially the possibility of inhibiting fibroblast function by alterations of the interaction between immunocompetent cells and fibroblasts would indicate a place for immunosuppressive therapy in SS (5). Our data on patients treated with cyclosporin A and prednisone with and without cyclophosphamide support this suggestion, although they do not allow any prefer-

**DISCUSSION**

The close correlation of serum PIIINP levels and skin involvement in SS is in good accordance with our preliminary data (8) and those of other workers (7,11,12). We found no correlation to the presence

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ence of one of these drugs. Pencillamine affects collagenolysis and cross linking (15). This, together with the fact that pencillamine was our drug of choice in type I and type II SS with a slow pace of extremity skin thickening, makes an evaluation and comparisons between pencillamine and the other treatment modalities difficult. The observed lower serum values of PIINP following pencillamine treatment could be due to the additional immunosuppressive effect of the drug.

Our study only reports on fibrogenesis related to type III collagen, but we believe that serum PIINP may be utilized as a marker of this type of fibrogenesis in SS and therefore is of prognostic value. Hermann et al. (16) recently investigated PIINP and laminin P1 serum levels together with acid lysosomal beta-galactosidase in SS and silicone-associated sclerosis. Increased PIINP strongly correlated with enhanced activity of beta-galactosidase and the clinical course in both groups, but although serum levels of laminin P1 were also elevated, there was no correlation with the severity of the disease. Recently, it has also become possible to study fibrogenesis of type I collagen by analysis of serum samples (17) for carboxyterminal propeptide of type I procollagen (PICP). We are at present studying the relationship between PIINP and PICP in the different subsets of SS and the relation to therapy.

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