IntroductIon

While several auto antibodies have been detected in patients with systemic lupus erythematosus (SLE), only antibodies against double stranded DNA (anti-dsDNA) and Sm antigen (anti-Sm) are considered to be SLE-specific. A similar role and clinical significance has been attributed to antibodies against ribosomal P protein (anti-P).

Ribosomal P protein is a pentamer consisting of 3 different phosphoproteins forming monomer P0 and dimers P1 and P2. It plays an important role in all stages of protein synthesis. Anti-P antibodies recognize at least 1 epitope common for all 3 phosphoproteins and are reactive with linear structure of antigenic determinant within their homologous C-terminal 22 amino acid sequence. The presence of anti-P antibodies might be associated with multiple organ involvement in the course of SLE, including the central nervous system (CSN), kidneys, or liver, but the results from various studies are still conflicting.

The aim of this study was to assess the frequency as well as clinical and serological relevance of anti-P auto antibodies in Polish patients with SLE and to determine the significance of these antibodies in the diagnosis of SLE.

INTRODUCTION

Antibodies against ribosomal P protein (anti-P) are detected predominantly in patients with systemic lupus erythematosus (SLE). However, the data on their frequency and clinical relevance remain inconclusive.

OBJECTIVES

The aim of the study was to assess the frequency as well as clinical and serological relevance of anti-P auto antibodies in Polish patients with SLE and to determine the significance of these antibodies in the diagnosis of SLE.

PATIENTS AND METHODS

Anti-P antibody levels were measured in the sera of 100 SLE patients using an enzyme-linked immunosorbent assay and Western blotting. All patients underwent a routine clinical and laboratory evaluation. Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score.

RESULTS

Anti-P antibodies were detected in 14 of 100 patients. When compared to anti-P-negative patients, this group was characterized by earlier onset of SLE, higher disease activity, more frequent occurrence of fever and facial erythema, decreased serum levels of complement, and elevated levels of alanine and aspartate aminotransferases. In 2 cases, anti-P antibodies were the only serological marker of SLE detected in these patients.

CONCLUSIONS

SLE with the presence of anti-P antibodies is characterized by an early onset and high disease activity.

KEY WORDS

antibodies against ribosomal P protein, disease activity, systemic lupus erythematosus

ABSTRACT

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The aim of this study was to assess the prevalence of anti-P antibodies among Polish patients with SLE, to characterize the clinical manifestation of this disease in a group of anti-P positive patients, and to define the role of anti-P in the diagnosis of SLE.

PATIENTS AND METHODS

The study included 100 women with SLE, consecutively admitted to
TABLE 1 Characteristics of SLE patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Anti-P/–/ (n=86)</th>
<th>Anti-P/+/ (n=14)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>age at disease onset (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;9 years</td>
<td>35.2 ±15.2a</td>
<td>27.9 ±16.4a</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>median: 33 (min. 10 – max. 70)</td>
<td>median: 23.5</td>
<td>(min. 11 – max. 70)</td>
<td></td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>4 (5%)</td>
<td>4 (29%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>16–44 years</td>
<td>58 (68%)</td>
<td>8 (57%)</td>
<td></td>
</tr>
<tr>
<td>&gt;45 years</td>
<td>23 (27%)</td>
<td>2 (14%)</td>
<td></td>
</tr>
<tr>
<td>age at time of study (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;9 years</td>
<td>40.8 ±14.9a</td>
<td>33.6 ±16.0a</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>median: 41 (min. 18 – max. 76)</td>
<td>median: 28</td>
<td>(min. 19 – max. 70)</td>
<td></td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>4 (5%)</td>
<td>2 (14%)</td>
<td></td>
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<td>16–44 years</td>
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<tr>
<td>&gt;45 years</td>
<td>23 (27%)</td>
<td>2 (14%)</td>
<td></td>
</tr>
<tr>
<td>disease duration (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;9 years</td>
<td>68.7 ±8.1b</td>
<td>82.1 ±25.4b</td>
<td>NS</td>
</tr>
<tr>
<td>median: 48 (min. 2 – max. 312)</td>
<td>median: 66</td>
<td>(min. 4 – max. 360)</td>
<td></td>
</tr>
<tr>
<td>&lt;3 years</td>
<td>41 (48%)</td>
<td>6 (43%)</td>
<td></td>
</tr>
<tr>
<td>3–9 years</td>
<td>27 (32%)</td>
<td>3 (21%)</td>
<td></td>
</tr>
<tr>
<td>&gt;9 years</td>
<td>17 (20%)</td>
<td>5 (36%)</td>
<td></td>
</tr>
</tbody>
</table>

a standard deviation
b standard error of mean

TABLE 1 Characteristics of SLE patients

**Results**

On the basis of the anti-P antibody measurement, 100 patients included in our study were classified into 2 groups, namely 86 patients with the negative result of anti-P tests (anti-P/–/) and 14 patients with the positive result (anti-P/+). TABLE 1 presents the characteristics of both patient groups.

Higher incidence of fever (51% vs. 86%, P <0.05) and malar rash (49% vs. 86%, P <0.05) was observed in the anti-P/+ group. Involvement of the nervous system was observed in 22 anti-P/–/ patients (psychoorganic syndrome in 2, depression in 8, convulsions in 4, stroke in 5, cranial nerves neuropathy in 2, polineuropathy in 1) and in 2 anti-P/+ patients (depression in 1, stroke in 1) (P = nonsignificant [NS]).

The 2 groups did not differ significantly with respect to either peripheral blood cell counts or the laboratory indicators of inflammation (ESR, CRP, α2-γ-globulin) (P = NS).

Interestingly, anti-P/+ patients had significantly higher levels of alanine and aspartate aminotransferases (9.5% vs. 36%, P <0.05). However, this increase was moderate and did not exceed twice the upper limit of the normal value. In isolated cases, an increase in aminotransferases was accompanied by elevated alkaline phosphatase and γ-glutamyltransferase. Moreover, routine abdominal ultrasound revealed enlarged liver and enhanced liver echogenicity in 3 anti-P/–/ and 2 anti-P/+ patients.

Alcohol abuse, infection, and pharmacological factors were excluded as possible causes of these symptoms. Antimitochondrial antibodies were negative in all studied patients.

Increased aminotransferases were detected in both (2 out of 2) anti-P/+ patients displaying signs or symptoms of the CNS involvement. In comparison, such increase was observed in only 2 out of 22 anti-P/–/ patients with neuropsychiatric symptoms (P <0.05).

Various antinuclear antibodies were positive in the majority of patients. Anti-P antibodies were accompanied most frequently by anti-dsDNA, anti-RNP, anti-Sm, and antithistone antibodies,
but none of these correlations achieved statistical significance (P = NS).

A significant decrease of C3 complement component was observed in anti-P/+ patients (71% vs. 29%, P < 0.05), while kidney involvement was associated more often with anti-dsDNA antibodies (50% vs. 22%, P < 0.05) (FIGURE 1).

In order to establish the diagnostic value of anti-P antibodies in SLE, we analyzed the frequency of marker antibodies (according to point 10 of SLE diagnostic criteria). Among 14 anti-P/+ patients only 1 displayed all 4 types of autoantibodies, 4 patients had anti-dsDNA and anti-Sm antibodies, 6 patients had only anti-dsDNA. There were a few cases of single antibody production, namely only anti-Sm or only antiphospholipid antibodies. Two anti-P/+ patients did not display any of the autoantibodies listed in point 10 of the diagnostic criteria.

The majority of anti-P/+ patients exhibited high disease activity (>20 points SLEDAI; 79% vs. 44%, P < 0.05) (FIGURE 2). Analysis of data by median test indicated that for 50% of anti-P/+ patients disease activity was above 23 points SLEDAI, while 50% of anti-P/− patients had SLEDAI score above 18 (P < 0.05) (TABLE 2).

Comparative analysis of SLE activity in both groups at the onset of the disease and during the course of this study revealed that while in the anti-P/− patients, the initially high disease activity eventually decreased significantly, in the anti-P/+ group it remained high.

**DISCUSSION**

Although discovered over 30 years ago, anti-P antibodies are still somewhat underestimated in the diagnosis of SLE, and there is no consensus regarding their correlation with clinical picture and their role in the pathogenesis of this disease.

Genetic and environmental factors are most likely responsible for the discrepancies in reported frequencies of anti-P in SLE patients. For example, 30% to 42% of SLE patients within Chinese and Japanese populations are anti-P positive.

Frequency of anti-P detected in this study reached 14%, which is in agreement with other studies conducted in the white population.

Strikingly, these antibodies are quite common in pediatric patients and young adults with SLE, reaching 20% to 42%. In line with these studies, almost 30% of our anti-P/+ patients developed SLE before the age of 15, and half before the age of 23. In contrast, 50% of patients in the anti-P/− group developed the disease before the age of 33, which represents a statistically significant difference (FIGURE 3).

Fever, skin lesions, and arthritis appeared to be the prevailing symptoms in our patients and were detected significantly more often in the anti-P/+ group (P < 0.05). Other authors reported even more frequent skin involvement in anti-P/+ patients, particularly malar rash, discoid lupus erythematosus, sensitivity to ultraviolet light, and cutaneous manifestations of vasculitis.

Concomitant occurrence of lupus nephritis and anti-dsDNA antibodies was twice as frequent in patients with anti-P/+ as in anti-P/− group, similarly to the results reported previously by others (FIGURE 1).

In 2 of the studied patients, serological abnormalities were limited to anti-P antibodies. As reported by other authors, 35% of anti-P/+ SLE patients do not have anti-dsDNA antibodies. It is postulated that anti-P can be a valuable serological marker of SLE and play an important role in a diagnostic process, being especially helpful in cases of SLE fulfilling any 4 diagnostic criteria with the exception of point 10, i.e., lack of marker antibodies.

In the present study, similarly to the previously published data, there was no relationship between anti-P and the CNS involvement.

The results of several studies suggest higher frequency of lupoid hepatitis in patients with anti-P antibodies. The term “lupoid hepatitis” was first used by I.R. Mackay in 1959 to describe chronic progressive hepatitis accompanied by serological disturbances typical for SLE. Currently,
this disease is classified as chronic active autoimmune hepatitis with antinuclear antibodies. Typically, autoimmune non-SLE-related chronic active hepatitis patients do not have anti-P antibodies, suggesting a potential use of anti-P in diagnostic differentiation of these 2 types of hepatitis.

Indeed, our experience confirms such a possibility, since the increased levels of liver enzymes were detected in 36% of anti-P/+ patients and only in 9.5% of anti-P/-/ patients. Moreover, in agreement with previous reports, we observed a link between neurological symptoms, an increase in aminotransferases and the presence of anti-P. 11,32

It was possible to gain better understanding of this correlation in the light of the studies by Koren et al. 33 and Koscec et al. 15 Ribosomal P protein has been reported to be expressed on the surface of cultured human hepatoma and neuroblastoma cells; furthermore, it has been confirmed that anti-P antibodies are able to bind to hepatoma cells, penetrate into live hepatocytes, and cause cellular dysfunction in vitro.

Anti-P antibodies are detected more frequently in SLE patients with concomitant anti-dsDNA and anti-Sm antibodies. It was demonstrated that both anti-P and anti-dsDNA antibodies are able to bind not only ribosomal P protein but also deoxyribonucleic acid. Anti-dsDNA antibodies have a cytotoxic potential and are sensitive to at least partial blocking with C-terminal peptide derived from protein P, or with recombinant protein P1. Since the expression of protein P is ubiquitous (fibroblasts, endothelial cells, lymphoid cells, liver and kidney cells) such interaction with anti-dsDNA antibodies may indeed play a significant role in the pathogenesis of SLE. 34,35 On the other hand, anti-P proved to be cross-reactive with other antibodies, such as anti-Sm and antiphospholipid 36,37

Activity of SLE measured by the SLEDAI score was significantly higher among anti-P/+ patients. 4,40 Comparative analysis of SLE activity in both groups at the onset of the disease and during this study revealed that it remained high in the anti-P/+ group of patients despite the treatment. It may imply more severe course of the disease and poorer response to therapy, especially when compared with the anti-P/-/ group, in which the initially high disease activity eventually decreased.

Anti-P antibodies constitute an important indicator of organ damage and disease activity in SLE. Detected mainly in SLE patients, these antibodies certainly deserve to be considered as markers of this disease as well as a valuable tool in diagnostic process. Results from experimental studies further corroborate their involvement in the pathogenesis of SLE.

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ARTYKUŁ ORYGINALNY

Obraz kliniczny tocznia rumieniowatego układowego u chorych z przeciwciałami przeciw rybosomальнemu białku P

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SŁOWA KLUCZOWE
aktywność choroby, przeciwciała przeciw rybosomальнemu białku P, toczń rumieniowaty układowy

STRESZCZENIE

WPROWADZENIE Przeciwciała przeciw rybosomальнemu białku P (anty-P) stwierdza się głównie u chorych na tocznię rumieniowaty układowy (systemic lupus erythematosus – SLE), ale dane na temat częstości ich występowania i korelacji klinicznych są niejednoznaczne.

CELE Celem badania była ocena częstości występowania, powiązań klinicznych i serologicznych przeciwciał anty-P u polskich chorych ze SLE oraz określenie ich znaczenia w ustaleniu rozpoznania SLE.

PACJENTI I METODY Przeciwciała anty-P oznaczono w surowicy 100 chorych na SLE za pomocą testu immunoenzymatycznego i Western blot. U wszystkich chorych przeprowadzono badanie lekarskie oraz rutynowe badania laboratoryjne. Aktywność choroby oceniono za pomocą skali SLEDAI (Systemic Lupus Erythematosus Disease Activity Index).

WYNIKI Przeciwciała anty-P wykryto u 14 spośród 100 chorych. W porównaniu z chorymi bez przeciwciał anty-P, grupa ta charakteryzowała się początkiem SLE w młodszym wieku, większą aktywnością choroby, częstszym występowaniem gorączki, rumienia na twarzy, hipokomplementemią oraz wzrostem stężenia transaminazy alaninowej i asparaginianowej. U 2 chorych przeciwciała anty-P były jedynym markerem serologicznym SLE.

WNIOSKI SLE z obecnymi przeciwciałami anty-P cechuje się początkiem choroby w młodzym wieku oraz wysoką aktywnością choroby.

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