PERIPHERAL B CELLS IMMUNOPHENOTYPING IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

Keywords: Systemic lupus erythematosus, Cell biology, Biomarkers

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Background: B cells play a central role in systemic lupus erythematosus (SLE) pathogenesis connecting innate with adaptive immunity.

Objectives: To investigate the peripheral blood B cell phenotype in a cohort of SLE patients with renal (LN-SLE) and non-renal (NR-SLE) involvement compared to healthy controls.

Methods: Ninety-nine SLE patients, 76 with active renal involvement (30 at disease onset-Early and 46 in whom LN occurred after the disease onset-Long) and 23 with non-renal disease (articular and/or cutaneous) were enrolled. Thirty-seven healthy controls were included. Clinical, laboratory and demographic data were collected at baseline and at 6 and 12 months of follow-up. Disease activity was recorded using SLEDAI-2K. The memory B cells immunophenotyping (IgD/CD27 classification) was analyzed in peripheral blood through flow cytometry. To clarify the role of key molecules in the B cells activation, IL-6 and BAFF serum levels were assessed by Enzyme-linked immunosorbent assay (ELISA).

Results: Studying the B cell subsets, a lower percentage of CD19+ and unswitched memory (IgD+/CD27-) in the whole SLE cohort compared to controls (8.7±4.8% vs 10.5±3.5%; p=0.002 and 10.7±13.7% vs 15.3±8.0%; p=0.01, respectively) was observed. In addition, we found higher levels of double-negative memory B cells (IgD+/CD27-) and plasmablasts (CD27+/CD38+) in SLE than in controls (CD27+/IgD+ 10.3±8.3% vs 4.1±1.19; p=0.01) (CD27+/CD38+ 6.1±7.9% vs 1.0±0.5%; p=0.01)). Furthermore, CD19+ negatively correlated with BAFF (r=0.32; p=0.01). No correlation was found between B cell subsets and the disease activity parameters. According to the organ involvement, LN-SLE and RN-SLE showed a lower percentage of CD19+ (IgD+/CD27-) and plasmacells and higher levels of IgD+/CD27- than controls ([CD19+], LN-SLE:9.1±74% vs 10.5±4.6%; p=0.005; NR-SLE: 7.7±4.6%; p=0.008) (IgD+/CD27-) LN-SLE:10.4±14.9% vs 15.3±8.0%; p=0.001; NR-SLE: 11.6±8.6%; p=0.006) (CD27+/CD38+), LN-SLE: 7.5±8.4% vs 9.0±5.5%; p=0.001; NR-SLE: 1.6±2.2%; p=0.001 (IgD+/CD27-) LN-SLE: 10.6±8.5% vs 4.1±1.9%; p=0.001; NR-SLE: 9.6±7.3%; p=0.006). According to the onset of renal symptoms, there were no differences in the distribution of the renal classes and in activity and chronicity indexes in the two groups. Analyzing the B cells subsets the Long-LN-SLE showed a lower percentage of CD19+ (IgD+/CD27-) and plasmacellular and higher levels of IgD+/CD27- than controls ([CD19+], LN-SLE:9.1±74% vs 10.5±4.6%; p=0.005; NR-SLE: 7.7±4.6%; p=0.008) (IgD+/CD27-) LN-SLE:10.4±14.9% vs 15.3±8.0%; p=0.001; NR-SLE: 11.6±8.6%; p=0.006) (CD27+/CD38+), LN-SLE: 7.5±8.4% vs 9.0±5.5%; p=0.001; NR-SLE: 1.6±2.2%; p=0.001 (IgD+/CD27-) LN-SLE: 10.6±8.5% vs 4.1±1.9%; p=0.001; NR-SLE: 9.6±7.3%; p=0.006). According to the onset of renal symptoms, there were no differences in the distribution of the renal classes and in activity and chronicity indexes in the two groups. Analyzing the B cells subsets the Long-LN-SLE showed a lower percentage of CD19+ and unswitched memory (IgD+/CD27-) compared to controls (6.6±8.5% vs 10.5±3.5%; p=0.004 and 9.7±8.9% vs 15.3±8.0%; p=0.001, respectively) and higher levels of IgD-/CD27+ (12.1±8.4%) than Early-LN-SLE (8.3±8.3%; p=0.027), NR-SLE (9.6±7.3% p=0.001) and controls (4.1±1.9%; p=0.001).

Furthermore, a direct correlation was observed between serum IL-6 levels and SLEDAI in Long-LN-SLE patients (r=0.38; p=0.004).

Conclusion: Data on memory B cells immunophenotyping reveals a distinct B cell subset of SLE patients when compared to healthy controls, confirming an activation of B cells subsets in SLE patients and strengthening the hypothesis of the pathogenetic role played by B lymphocytes in the course of LN. In particular, the higher levels of DN B cells observed in patients in which renal damage occurs after the onset of SLE reinforcing the data that these cells represents a B memory subsets characteristic of immune system overactivation conditions.


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INDIRECT HEALTH RELATED COST IN PSS PATIENTS IN RELATION TO SYMPTOM BASED ENDOTYPES

Keywords: Patient reported outcomes, Work-related issues, Sjögren syndrome

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Background: Among the extra-glandular symptoms in primary sjögren’s syndrome (pSS), fatigue and pain are the most common. Fatigue is a poorly understood phenomenon with multi-faceded involvement. Therefore, it is important to assess the severity of fatigue and describe its various dimensions while assessing fatigue. On the other hand, fatigue is also one of the predictors of reduced health and quality of life in pSS.

Objectives: To assess fatigue by Fatigue Severity Scale (FSS) and Profile of fatigue (ProF) questionnaires and quality of life (QoL) with Health Assessment Questionnaire- Disability Index (HAQ-DI) and to know the association between the two in patients with pSS.

Methods: Patients fulfilling AECG 2002 and/or ACR-EULAR 2016 classification criteria for pSS were included in this prospective observational study between January 2021 to June 2022. Fatigue was assessed with FSS and ProF and QoL was assessed with HAQ-DI. Depression and somatoform disorder were assessed using PHQ9 and PHQ15 respectively. Associations with fatigue was compared using multivariate regression analysis. Written informed consent was obtained from all subjects included in the study and the study was approved by Institute Ethics Committee.

Results: Out of 125 patients, 114 (91.2%) were female and 11 (8.8%) were male with a female to male ratio of 9.6: 1. The median age at the time of inclusion into the study was 41(32-50) years. The median duration of the disease was 36 (12-60) months. The median ESSDAI and ESSPRI score were 2 (1-3) and 6 (2-9) respectively. Fifty seven (45.6%) patients had fatigue, defined as FSS of ≥4 and/or ProF ≥2 in either of the domains. Among the patients with fatigue, 12 (21%) patients scored less than 4 on FSS, 36 (63.1%) had mild fatigue, 7 (12.2%) had moderate fatigue and only 2 (3.5%) patients had severe fatigue. The mean FSS score in the cohort was 2.9 ± 1.5. The ProF mean scores were 2.7 ± 0.6 for somatic fatigue and 2.9 ± 1.3 for mental fatigue. The median HAQ-DI in patients with fatigue was significantly more compared to non-fatigue patients (0.1 vs 0.5; p <0.001; Figure 1). There was a positive correlation between fatigue score and HAQ-DI score (p=r 0.36, n = 125, p = <0.001). The prevalence of depression and somatoform disorder were 15.2% and 28% respectively. The ESSPRI pain score, ProFAD Ocular & Oral dryness score and PHQ-9 score were positively associated with higher fatigue score.

Conclusion: Fatigue was seen in nearly half of the patients with pSS and patients with fatigue had impaired QoL as assessed by HAQ-DI. The pain, dryness and presence of depression are the predictors of fatigue in patients with pSS.

REFERENCES: NIL.

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Background: Primary Sjögren’s Syndrome (pSS) is characterised by oral and ocular dryness, possible development of systemic manifestations, increased lymphoma risk, and a highly diverse patient burden. To address this heterogeneity, Tarn et al. identified four endotypes based on patient-reported symptoms of dryness, fatigue, pain, anxiety and depression: low symptom burden (LSB), pain dominant with fatigue (PDF), dryness dominant with fatigue (DDF) and high symptom burden (HSB). (1)

Objectives: The aim of this study was to explore indirect health related costs in relation to symptom-based endotypes in a cohort of patients with definite and suspected pSS.

Methods: Data from the Belgian Sjögren’s Syndrome Transition Trial (BeSSTT) was used in which patients positive for at least one of the 2016 ACR/EULAR classification criteria were enrolled. Patients were considered ‘definite pSS’ when fulfilling these criteria, and ‘suspected pSS’ otherwise. The Newcastle Sjögren’s Stratification Tool (NSST), developed and provided by Tarn et al., was applied to stratify the cohort into endotypes. Patients reported their current work status and sick leave in the past year and completed the Work Productivity and Activity Impairment questionnaire (WPAI).

Results: Application of the NSST tool resulted in 4 endotypes, both in definite (LSB n=23, DDF n=33, PDF n=82, HSB n=30) and suspected pSS (LSB n=14, DDF n=22, PDF n=48, HSB n=21). The majority of definite pSS patients were female (158, 88.8%) with a meansSD age of 53.4±14.7, with no significant differences between endotypes (p=0.365 and p=0.415). Definite pSS LSB patients reported significantly less invalidity (p=0.020). A numerically higher proportion of working PDF and HSB patients reported part time employment due to health (p=0.063). However, reported working hours did not differ between endotypes. In contrast, HSB pSS patients reported significantly more productivity loss during their job than those with LSB and DDF endotypes (p<0.001), which led to a significantly higher total work impairment (p<0.001). In addition, definite pSS patients with LSB endotype reported significantly more productivity loss during daily activities besides their job (69%, p<0.001). No significant differences concerning job characteristics were observed between definite and suspected pSS patients with the same endotype.

Conclusion: Definite pSS patients with a LSB endotype encounter significantly more work impairment than those with other endotypes, which is due to a significantly higher productivity loss while working. In addition, these patients report significantly more productivity loss during daily activities besides paid work, which entails large indirect health related costs as pSS is a predominantly female disease. Moreover, the burden associated with the HSB endotype appears to influence work ability independent of a definite pSS diagnosis.

REFERENCE:

Table 1. Job characteristics of definite pSS patients per endotype.

<table>
<thead>
<tr>
<th>Definite pSS without job</th>
<th>LSB (n=10)</th>
<th>DDF (n=18)</th>
<th>PDF (n=44)</th>
<th>HSB (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Student/retired</td>
<td>10 (100.0)</td>
<td>9 (50.0)</td>
<td>17 (38.6)</td>
<td>6 (35.3)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>0</td>
<td>5 (27.8)</td>
<td>6 (13.6)</td>
<td>5 (29.4)</td>
</tr>
<tr>
<td>Invalidity</td>
<td>0</td>
<td>4 (22.2)</td>
<td>21 (47.7)</td>
<td>6 (35.3)</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td></td>
<td></td>
<td>0.020</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Definite pSS with current job</th>
<th>LSB (n=13)</th>
<th>DDF (n=15)</th>
<th>PDF (n=38)</th>
<th>HSB (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part time due to health</td>
<td>1 (7.7)</td>
<td>4 (26.7)</td>
<td>20 (52.6)</td>
<td>7 (53.8)</td>
</tr>
<tr>
<td>Working hours per week</td>
<td>0 (0.0)</td>
<td>3.9 (9.4)</td>
<td>3.0 (7.5)</td>
<td>3.1 (6.9)</td>
</tr>
<tr>
<td>Absent: health</td>
<td>6.5 (117)</td>
<td>7.3 (17.1)</td>
<td>3.8 (7.8)</td>
<td>13.7 (30.8)</td>
</tr>
<tr>
<td>Absent: other</td>
<td>28.7 (13.6)</td>
<td>30.5 (10.5)</td>
<td>22.0 (14.1)</td>
<td>28.8 (15.0)</td>
</tr>
<tr>
<td>Worked</td>
<td>0.12 (0.18)</td>
<td>0.17 (0.21)</td>
<td>0.34 (0.29)</td>
<td>0.60 (0.20)</td>
</tr>
<tr>
<td>Lost productivity due to health</td>
<td>0.1 (0.1)</td>
<td>0.2 (0.2)</td>
<td>0.3 (0.3)</td>
<td>0.6 (0.2)</td>
</tr>
</tbody>
</table>

Figure 1. Boxplot visualizing total work impairment, assessed by WPAI, of definite and suspected pSS patients in relation to symptom-based endotypes. A score of 0.00 indicates no impairment, while 1.00 corresponds with total impairment.

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AB0562

HISTOLOGICAL RENAL FEATURES AND CYTOKINES ASSESSMENT AS POSSIBLE BIOMARKERS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND LUPUS NEPHRITIS

Keywords: Biomarkers, Cell biology, Systemic lupus erythematosus

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Background: Lupus Nephritis (LN) management remains a challenge for the inadequacy of the traditional parameters in identifying more severe disease and preventing renal damage.

Objectives: To identify a multipanel biomarkers matrix, from histological to molecular level, aiming to improve prognostic stratification and therapeutic protocol of LN patients.

Methods: 45 SLE patients with active disease (age: 40.5 ± 11.0 years) at disease onset or at disease flare were enrolled. 6 patients with LN in persistent remission (R-LN) (age: 43.5 ± 11.9 years) were included as controls. 28 patients had an active LN and underwent ultrasound-guided renal biopsy while 15 patients with non-renal SLE (NR-SLE) displayed cutaneous or articular manifestations. Laboratory, immunological and disease activity data were collected at baseline and then at 6(T6) and 12(T12) months. Renal biopsies were evaluated according to ISN/RPS classification, assessing the activity and chronicity index and the active interstitial infiltrate (II) using the BANFF score system. Serum level of BAFF, IL-2, L6, IL-17 and IFN-α were assayed in the study cohort by ELISA panel at each timepoint.

Results: Considering LN cohort, 66% of the renal biologies belonged to class III and IV; 71.8% of LN patients had a II>5%. Performing univariate analysis for each renal outcome, focusing on histological assessment, a significant association between higher activity index and worse renal prognosis in terms of remission achievement at 12 months (p<0.04), proteinuria and chronic renal damage development (p=0.04 and p=0.03 respectively) was observed. Through the ROC curve analysis, a cut-off value of activity index of 7.5 was identified (sensitivity 72.7%, specificity 66.7%) [AUC: 0.77; 95% CI, 0.56-0.98; p= 0.04] for remission achievement within 12 months and proteinuria development. Furthermore, LN patients with presence of II>5% were not only less likely to achieve early remission (p=0.04) as well as those with at least one antiphospholipid antibody (Apl+) positivity (p=0.05), but displayed a worse renal outcome overall, though without reaching statistical significance. The analysis of circulating cytokines revealed that serum levels of IL-6 were significantly higher in patients with active disease as compared to R-LN patients, independently from renal involvement (LN: 7.6 ± 10.0 vs R-LN: 2.1 ± 2.1, p=0.02; NR-SLE: 11.4 ± 17.8 vs R-LN: 2.1 ± 2.1, p=0.02). Moreover, baseline serum level of IFNα was significantly increased in LN patients compared to R-LN (12.1 ± 36.8 vs 1.5 ± 3.6, p=0.01). Serum levels of IL-6 in LN patients positively correlated with disease activity index (R=0.819; p<0.001), and negatively with C3 (R=-0.608; p=0.003) and C4 (R=-0.675; p=0.001). Furthermore, serum levels of IL-6 were associated with histological severity being significantly higher in patients with II>5% (p<0.01) and positively correlating with activity index (R=0.655; p=0.01). The evaluation of cytokines serum levels in relation to outcome achievement revealed that NR-SLE patients with favorable course had baseline higher serum level of IL-2 than those with active disease (0.6 ± 0.2 vs 0.1 ± 0.1, p=0.01). Finally, LN patients with higher serum levels of IL-6 during the follow-up were less likely to reach remission (3.7 ± 1.8 vs 2.1 ± 1.4, p=0.02) as well as LN patients with higher serum level of IL-17 (3.4 ± 8.0 vs 0.9 ± 0.3, p=0.01). In particular, higher baseline serum levels of IL-17 were observed in patients who developed persistent proteinuria than those who did not (2.3 ± 2.3 vs 0.7 ± 0.5, p=0.02) and tended to remain higher also during FU, together with IL-6 serum level.

Conclusion: II>5%, higher disease activity index and Apl+ represent in our study the strongest predictors of worse renal outcome, among traditional parameters. Higher IL-6 and IL-17 serum levels, at baseline and during FU, emerge as negative prognostic factor suggesting a possible role as biomarkers of more aggressive LN. IL-2 seems to have a protective role in extra renal disease.

REFERENCES: NIL.

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