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NEUTROPHIL ACTIVATION IDENTIFIES PATIENTS WITH ACTIVE POLYARTICULAR GOUT – A NOVEL BIOMARKER?

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Background: Neutrophils are key immune cells participating in host defense through several mechanisms, including the formation of neutrophil extracellular traps (NETs). Although beneficial from a host-pathogen perspective, excessive neutrophil activation has been linked to inflammation and autoimmunity, including systemic lupus erythematosus (SLE) and gout. In gout models, uric acid crystals induce NETosis. Though NETs are known to induce marked inflammation through TLR9- and cGAS- dependent pathways, as well as partake in induction of tissue damage and thrombotic events, the role of NETs in human gout has not been carefully investigated.

Objectives: Our objective is to investigate evidence of systemic neutrophil activation, and the clinical utility of neutrophil-derived biomarkers in gout. We hypothesize that uric acid crystals will activate neutrophils to undergo NET formation, with these processes contributing to immune cell activation, and local joint destruction.

Methods: Plasma samples from 75 gout patients participating in the ‘Reade gout cohort Amsterdam’ were compared with 30 healthy controls (HC). Levels of NETs, and NET-derived markers (cell-free DNA and peroxidase activity) were analyzed using a MPO-DNA ELISA, as well as fluorescence (2) Levels of calprotectin (S100A8/A9) were analyzed by ELISA, Mitochondrial (mt, COXII), as well as genomic (n, RPLP0) DNA levels were analyzed by qPCR. All of the analyzed markers were compared between gout patients and healthy individuals, and related to markers of inflammation and disease activity.

Results: Levels of NETs, as well as other neutrophil biomarkers, were significantly increased in gout patients as compared to healthy subjects (p<0.01, Figure 1A). In contrast to SLE, gout patients did not have elevated levels of circulating mtDNA (p=0.96), but only nDNA (p=0.006). No associations were found between markers of cell death (cDNA and NETs) and disease activity. Peroxidase activity correlated with disease activity (RAPID score: r=0.43, p=0.01, RAPID function: r=0.54, p=0.001) and inflammation markers (CRP: r=0.40, p=0.001, and ESR: r=0.43, p=0.001). Involvement of ankle and wrist resulted in significant higher peroxidase levels compared to mono-articular disease (p=0.01, and p<0.03, respectively), suggesting peroxidase activity being a marker of polyarticular gout (Figure 1B). Calprotectin (S100A8/A9) correlated with the inflammation markers CRP and ESR (r=0.30, p=0.01, and r=0.30, p=0.001, respectively) and morning stiffness, especially in patients with chronic polyarticular gout (p=0.61, p=0.001).

Conclusion: To our knowledge, this is the first report demonstrating presence of NETs in the peripheral blood of gout patients. Although markedly elevated, levels of NETs did not associate with markers of disease activity or inflammation, possibly due to the lack of inflammatory mitochondrial DNA within the NETs. Even so, our data demonstrate an important role of neutrophils in gout pathogenesis, with neutrophil activation markers associating with characteristics of active, and more pronounced polyarticular disease.

REFERENCES

PREGNANCY SUCCESS RATE AND RESPONSE TO HEPARINS AND/OR ASPIRIN DIFFERS IN WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS ACCORDING TO THE GAPSS SCORE

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Background: Current standard of care (SoC) in pregnancy for patients with Systemic lupus erythematosus (SLE) and/or aPL positivity includes treatment with low dose aspirin (75–100mg/day) and low molecular heparin or unfractionated heparin. However, up to 30% of women continue to have pregnancy complications despite SoC. Therefore, identifying patients that are at greater risk to develop pregnancy complications despite the SoC and might benefit from additional therapeutic approaches, is still an unmet clinical need.

Recently, our group conceived and validated the global antiphospholipid syndrome score (GAPSS) [1], as a risk score for predicting aPL-related clinical manifestations (thrombotic and/or pregnancy morbidity).

Objectives: We aimed to investigate response to SoC in women with SLE and/or aPL positivity when stratifying their risk according to GAPSS Score.

Methods: 143 women ever pregnant treated with SoC therapy with SLE and/or aPL positivity were included. Data on cardiovascular risk factors and SoC and might benefit from additional therapeutic approaches, is still an unmet clinical need.

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Objectives: We aimed to investigate response to SoC in women with SLE and/or aPL positivity when stratifying their risk according to GAPSS Score.

Methods: 143 women ever pregnant treated with SoC therapy with SLE and/or aPL positivity were included. Data on cardiovascular risk factors and aPL positivity were retrospectively collected. The individual GAPSS score was calculated for each patient by calculating the sum of each risk factor (1: arterial hypertension, 2: dyslipidemia, 3: diabetes, 4: smoking status, 5: chronic renal disease, 6: atrial fibrillation, 7: history of DVT or PE, 8: history of myocardial infarction or stroke, 9: history of systemic lupus erythematosus (SLE) and/or aPL positivity). The GAPSS score was retrospectively calculated and the women were divided into three groups: GAPSS <6, 6–12, or ≥13. The primary outcome measure was pregnancy success rate, defined as the absence of pregnancy complications.

Results: The analysis included 143 patients (mean age 30.8 ±6.4) with SLE (122; 85.3%) and/or aPL positivity, for a total of 352 pregnancies. Our results showed that women with a GAPSS score of 6–12 had a lower pregnancy success rate compared to women with a GAPSS score of 0–5 (31.9% vs 86.2%, p=0.001). In contrast, women with a GAPSS score of ≥13 had a higher pregnancy success rate compared to women with a GAPSS score of 0–5 (86.7% vs 86.2%, p=0.75).

Conclusion: Our study confirms the importance of the GAPSS score in predicting pregnancy success in women with SLE and/or aPL positivity. Women with a higher GAPSS score are at increased risk of pregnancy complications, and may benefit from additional therapeutic approaches. Further research is needed to validate the utility of the GAPSS score in clinical practice.
The main objective of this analysis was to investigate the relevance of structural improvement, if any, in DMOAD trials. Anxiety and depression (AD) disorders are known to affect pain sensitivity and perception, and as common co-morbidities of OA, these conditions may counterintuitively, mild structural disease may be associated with severe symptoms and vice versa. Research to uncover factors distorting the perceived severity of symptoms is needed to better characterize the clinical relevance of structural improvement, if any, in DMOAD trials.

Result: In the AD group, 149 patients had AD in medical history of which 123 reported the condition as ongoing at baseline. The study groups of AD and matched controls (MC) were comparable in terms of age, sex, BMI, JSW, KL-grade and WOMAC pain. Associations between pain and JSW in the AD group, no significant correlation between JSW and WOMAC pain score was found, while BMI was found to be weakly associated with WOMAC pain (R= 0.19, p=0.02) in the multiple regression analysis. In the MC group, a statistically significant (p<0.004), correlation (R= -0.24) was found between JSW and pain indicating that lower JSW was associated with higher pain, with JSW accounting for approximately 6% of the total natural variation behind reported pain. In addition, a positive significant association between male sex and WOMAC pain (R=0.18, p=0.04) was found. The univariate linear relationship between JSW and pain is illustrated in Figure 1, and multivariate analyses are shown in Table 1.

Table 1. Associations between WOMAC pain, JSW (in red) and other baseline covariates

<table>
<thead>
<tr>
<th>Anx/Dep. group</th>
<th>Control group</th>
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<tbody>
<tr>
<td>f_{partial}</td>
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<tr>
<td>Age</td>
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</tr>
<tr>
<td>BMI</td>
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</tr>
<tr>
<td>Male Sex</td>
<td>0.10</td>
</tr>
<tr>
<td>JSW</td>
<td>0.03</td>
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Associations between pain and KL-Grade In the model evaluating associations between KL-grade and symptoms, there was no correlation between KL-grade and symptoms in the AD group. Similar to the findings relating to JSW, in the MC group, a weak (R=0.16), borderline

Figure. Linear correlations between WOMAC pain and JSW, with Spearman’s R reported.