Results: 45 patients with Farber disease (27 living, 18 deceased) who had or had not undergone hematopoietic stem cell transplant (HSCT) were enrolled from 16 centers in 9 countries. A cohort of 24 living non-HSCT patients were followed prospectively. The patients represented the broad phenotypic spectrum of Farber disease, from rapidly progressive (severe) to slowly progressive (atenuated). In patients whose data was available for analysis, the average age of patients at enrollment was 72 years (range 1 to 28 years). The average age of onset of joint disease (arthritis and/or contractures) was 15 months (range 3 months to 7 years), of subcutaneous nodules was 13 months (range 3 months to 5 years), and of dysphonia was 13 months (range birth to 8 years). The average time from onset of symptoms to Farber disease diagnosis was 2 years (range <1 to 12 years). At baseline, the mean number of joints affected with active arthritis was 113 (range 0-36) and the mean number affected with contractures was 18 (range 0-38). 12.5% of patients were reported to have a bone disorder such as osteoporosis or osteotomy. The Child Health Assessment Questionnaire Disability Index (CHAQ) ranging from 0 (no impairment) to 3 (unable to do) was high, with mean scores of 2.62-3.00 across visits.

Conclusion: Data from the Farber disease natural history study further defined the cardinal symptoms, phenotypic spectrum, and high disease-related burden in patients with Farber disease. The large number of joints affected with arthritis or contractures reflects that patients with Farber disease are often referred to rheumatology and can be misdiagnosed with polyarticular juvenile idiopathic arthritis or seronegative rheumatoid arthritis. Demographic information and numbers of patients enrolled indicate that Farber disease is likely not as rare as previously thought. ASAH1 genetic testing for adult and pediatric patients referred to the rheumatology clinic with symptoms including polyarticular arthritis, subcutaneous nodules, dysphonia, or osteotomy, may shorten the time to diagnosis in patients with Farber disease.

Disclosure of Interests: Lothar Seefeldt Speakers bureau: Acoregen, Amgen, Alexion, Biocareena, Chiesi, Evotec, KyowaKiren, Novartis, Theranex, and UCSB, Grant/research support from: Alexion, KyowaKiren and Novartis, Kathleen Crosby Employee of: Acoregen, Alexander Solyom Employee of: Acoregen


Table 1. Clinical and laboratory features of pts with FMF-AA according to AA-a burden

<table>
<thead>
<tr>
<th>Variables</th>
<th>G1 (n=79)</th>
<th>G2 (n=20)</th>
<th>G3 (n=14)</th>
<th>p1 (OR)</th>
<th>p2</th>
<th>p3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>42.8±13</td>
<td>43.2±13</td>
<td>48.9±11</td>
<td>0.9</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Gender, male**</td>
<td>36 (45.6)</td>
<td>15 (75)</td>
<td>7 (50)</td>
<td>0.02</td>
<td>0.8</td>
<td>0.1</td>
</tr>
<tr>
<td>Diagnosis age of AA-a *</td>
<td>30.7±13</td>
<td>34.1±14</td>
<td>34.9±15</td>
<td>0.3</td>
<td>0.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Duration of AA-a *</td>
<td>13.8±9</td>
<td>10.8±6</td>
<td>14.3±8</td>
<td>0.15</td>
<td>0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Baseline</td>
<td>CRP (mg/L)</td>
<td>20±13</td>
<td>24±19</td>
<td>13±7</td>
<td>0.4</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>P1-acutn II</td>
<td>3.8±6</td>
<td>12.4±16</td>
<td>5.4±2</td>
<td>0.03</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>e-GFR (ml)</td>
<td>8±0.4</td>
<td>1.5±8.1</td>
<td>1.8±3</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>e-GFR (ml)</td>
<td>10±4.3</td>
<td>11±3.4</td>
<td>13.2±9</td>
<td>0.02</td>
<td>0.04</td>
</tr>
<tr>
<td>CRP at admission**</td>
<td>28.7±40</td>
<td>16.1±36</td>
<td>11.6±23</td>
<td>0.02</td>
<td>0.03</td>
<td>0.6</td>
</tr>
<tr>
<td>Duration of bLYMDAR</td>
<td>6±5.2</td>
<td>7±5.2</td>
<td>13±5.2</td>
<td>0.7</td>
<td>0.01</td>
<td>(1)</td>
</tr>
<tr>
<td>Mortality</td>
<td>8 (10)</td>
<td>3 (5)</td>
<td>15 (20)</td>
<td>0.05</td>
<td>0.06</td>
<td>(10)</td>
</tr>
</tbody>
</table>

Table 1. Clinical and laboratory features of pts with FMF-AA according to AA-a burden

Figure 1. Comparison of survival rate between G3 and G1Log-Rank: p=0.007

<table>
<thead>
<tr>
<th>POS0224</th>
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<tbody>
<tr>
<td>AMYLOID BURDEN AND ASSOCIATED FACTORS PREDICT HIGHER MORTALITY AND POOR OUTCOME IN FAMILIAL MEDITERRANEAN FEVER-ASSOCIATED AA AMYLOIDOSIS: DATA FROM A TERTIARY REFERRAL AMYLOIDOSIS CENTER WITH 137 PATIENTS</td>
</tr>
</tbody>
</table>

M. Bektas¹, N. Koca¹, E. Oguz¹, B. Inci¹, S. San¹, N. Sentürk¹, Y. Yalçınkaya¹, B. Arım-Esen¹, M. Inanc¹, A. Gül¹, ¹Istanbul Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Istanbul, Turkey; ²Istanbul Faculty of Medicine, Department of Internal Medicine, Istanbul, Turkey

Background: AA amyloidosis (AA-a) is a rare condition while the most common cause is Familial Mediterranean Fever (FMF) in Turkey. There is limited evidence about the impact of AA-a burden on prognosis and outcome in AA-a.

Objectives: We herein aimed to evaluate the AA-a burden and its association with outcome in patients (pts) with FMF-associated AA-a (FMF-AA).

Methods: We retrospectively evaluated FMF-AA pts from our AA-a cohort. Diagnosis of AA-a was confirmed by histologically. Heart involvement (inv.) was defined by documenting increased (>12 mm) septal wall thickness (CSWT) and at least one of three appropriate echocardiography findings (decreased ejection fraction, increased granular echocarphy or valvulopathy, diastolic dysfunction). The pts were divided in three groups according to AA-a burden: pts had only renal inv. (Group 1), renal and gastrointestinal (GIS) (Group 2); renal and GIS and heart (Group 3).

Results: Data of 137 pts with FMF-AA (55% male) were analyzed. We classified 79 pts in G1, 20 in G2, and 14 in G3. CSWT, troponin (top) and pro-BNP levels were higher in G3 than G1 and G2 but trop levels were not statistically (sts) significant (sig.) between G3 and G2. Overall mortality was in 15.3 %. While mortality rate increased gradually with higher AA-a burden (10 % in G1, 15 % in G2 and 43 % in G3), the difference was sts sig. between G3 and G1. The number of MEFV variants was lower in pts with higher AA-a burden, especially those with M694V homozygosity were 93% and 71% in G1, 83% and 67% in G2, and 75% and 50% in G3 rpp; but the differences were not sts sig. (p=0.2 and p=0.7 for G1-G2, p=0.06 and p=0.2 for G1-G3, p=0.6 and p=0.4 for G2-G3). The number of organ inv. was correlated with CSWT (n=0.59 )<0.001), trop (n=0.646), pro-BNP (n=0.572'), bsl creatinine (Cre) (n=0.511'), bsl proteinuria (prt) levels (n=0.321 p=0.008) and negatively correlated with bsl e-GFR (n=0.437') and biologic DMARD duration (n=0.235 p=0.03)

ROC analyses revealed 56% sensitivity (SS) and 70 % specificity (SP) for bsl Cre (cut off value [COV]0.95, AUC=0.726 p=0.02 95% CI 0.66-0.93), 83 % SS and 74 % SP for trop (COV 35.5 AUC=0.864 p=0.006 CI 0.73-0.99), 100 % SS and 85.5 % SP for pro-BNP (COV 7246 AUC=0.897 p=0.024 CI 0.79-1.0), 79% SS and 58 % SP for CSWT (COV 11.5 AUC=0.727 p=0.007 CI 0.61-0.84) to be able to predict higher mortality.

Conclusion: This study showed the association of AA-a burden with higher morbidity such as ESRD and higher mortality in pts with FMF-AA. Bsl Cre, prt and pro-BNP levels were correlated with extent of AA-a burden and predicted higher mortality. Lower frequency of pts with two exon 10 variants or M694V homozygosity in pts with higher AA-a burden indicates that additional genetic and environmental factors may play a role in the development and progression of AA-a in FMF.

<table>
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<tr>
<td>A NOVEL TNFRSF1A MUTATION ASSOCIATED WITH TNF-RECEPTOR ASSOCIATED PERIODIC SYNDROME AND ITS METABOLIC SIGNATURE</td>
</tr>
</tbody>
</table>

J. Steiner¹, A. Antebi¹, A. Annibal¹, T. Kubacki², ¹Max Planck Institute, Max Planck Institute for Biology of Ageing, Cologne, Germany; ²University Hospital Cologne, Cologne, Germany

Background: Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is an autosomal dominant syndrome characterized by prolonged episodes of fever, arthralgia, myalgia, abdominal pain and erythema-tous rash. 1 We report a new mutation in the TNFRSF1A gene which is associated with TRAPS and AA-amyloidosis. Furthermore we analyzed the metabolic changes using a metabolomics approach.

Objectives: To describe a novel mutation in the TNFRSF1A gene that causes TRAPS and AA-amyloidosis.

Methods: Case series. For pathogenicity predictions we used the PolyPhen-2 web-software2 and PROVEAN3. Metabolomics: Mass spectrometry was performed.

Disclosue of Interests: None declared


Scientific Abstracts

on patient plasma and healthy controls using an UHPLC system (Vanquish, Thermo Fisher Scientific, Bremen, Germany) coupled to an HRAM mass spectrometer (Q-Exactive Plus, Thermo Fischer Scientific GmbH, Bremen, Germany).

Results: A 44-year-old man (patient 1) presented to our hospital with abdominal pain, elevated inflammation parameters, renal failure and large proteinuria. Renal biopsy revealed AA amyloidosis. Further anamnesis showed he had suffered from recurrent attacks of abdominal pain with fever and elevation of inflammation markers since he was 16 years old. He also reported that his father, aunt, sister and daughter have had similar problems. His daughter (patient 2) reported recurrent episodes of abdominal pain. Since she was 11 years old and his 46-year-old sister (patient 3) reported similar symptoms starting at 12 years of age. Upon presentation patient 3 showed proteinuria of 2000 mg/g creatinine (albuminuria 1500 mg/g creatine) strongly indicating early renal AA-amyloidosis. All symptomatic family members underwent genetic testing that revealed the yet uncharacterized TNFRSF1A-variant c.332A>G (p.Q111R). In silico analysis of the mutation by PolyPhen2 software and PROVEAN classified the mutation as probably pathogenic culminating in the diagnosis of TRAPS. All patients received canakinumab for treatment and responded with normalization of the inflammatory parameters. Patient 3 showed a marked reduction of proteinuria after 6 months of treatment. Using a metabolomics approach we were able to detect 158 distinct metabolic compounds of which 32 were up- and 35 downregulated, respectively. Two patients were analyzed before and after treatment with canakinumab. The treatment with canakinumab, however, appears to have no effect on the metabolic changes caused by TRAPS. Significantly upregulated metabolic pathways included purine metabolism, glycolysis/gluconeogenesis, glutathione metabolism, pyrimidine metabolism, arginine biosynthesis among others.

Conclusion: Here we present a novel mutation in the TNFRSF1A gene that causes TRAPS and is associated with AA-amyloidosis. Canakinumab is an effective treatment in this variant and led to improvement in proteinuria in one of the patients with presumed early renal AA-amyloidosis. We observed significant changes in the metabolite in comparison to healthy controls. Treatment with canakinumab appeared to have no effect on these metabolic changes caused by TRAPS.

References:

Disclosure of Interests: None declared.


Remodelling in OA

**POS022**

**FLUIDIC SHEAR STRESS REDUCES TNF-α MEDIATED CARTILAGE DAMAGE IN A 3D MODEL OF DEGENERATIVE JOINT DISEASE**

A. Damerau1 on behalf of AG Buttgeiret.

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2. Sanofi-Aventis Deutschland GmbH, Immunology & Inflammation Research, Frankfurt am Main, Germany

Background: Pathomechanisms of degenerative joint diseases such as osteoarthritis (OA) ultimately result in the breakdown of cartilage tissue. To date, the exact understanding of the mechanisms of both cause and progression of OA remain unclear. Therefore, developing complex and long-lasting in vitro components of a human joint including cartilage, subchondral bone, synovial membrane and tendons that simulate the 3D architecture and the metabolic, hormonal and cellular interplay of the joint components is needed to study the long-lasting course of OA pathogenesis. Beside the impact of metabolic components and 3D architecture, mechanical forces are well-known to be important modulators of joint health, while aberrant forces are primary etiological factors leading to cartilage degeneration.

Objectives: Here, we aimed to (i) develop a long-lasting human in vitro 3D cartilage model using alternated perfused cultivation and (ii) simulate TNF-α-mediated cartilage degradation. As a mechanical force we used the perfusion-mediated fluid shear stress (FSS) to enhance chondrogenesis and mimic FSS during joint movement.

Methods: Human bone marrow-derived mesenchymal stromal cells (MSC) were used to develop an in vitro 3D cartilage model incubated in a bioreactor with a perfusion cycle that facilitates mechanical stimulation via FSS and daily sampling. Within the bioreactor, MSC mass cultures were subjected to FSS at 10 dyn/cm² by medium circulation three times a day for 1.5 hours. The approach of using optimized FSS rate, cycles and cultivation period of 18 days for MSC mass cultures was compared to a non-perfused control based on cell viability (live-dead and viability-assay), apoptosis (TUNEL-assay, caspase-3/7-activity, BCL2/BAX), metabolic activity (oxygen and glucose consumption, lactate production), chondrogenic gene expression (ACAN, COMP, COL2A1, COL1A1, COL2A1/ COL1A1) and matrix metalloproteinase expression (MMP-1, -3, -13).

Results: Alternate perfused long-term cultivation at 10 dyn/cm² did not affect cell survival; it rather reduced apoptosis, did not affect oxygen consumption but reduced glucose consumption and lactate production and enhanced chondrogenic gene expression with reduced MMP13 and COMP gene expression compared to non-perfused conditions. Mimicking pathophysiology of OA we stimulated the 3D cartilage model with 100 ng/mL TNF-α for 6 hours under non-perfused and perfused long-term cultivation with FSS at 10 dyn/cm² as a mechanical stimulus. Compared to untreated perfused conditions, TNF-α stimulation (i) did not affect overall cell survival but enhanced apoptosis (demonstrating efficiency of stimulation), (ii) did not affect oxygen consumption (i.e. enhanced aerobic glycolysis), (iii) downregulated TNF-α expression as markers of matrix protein turnover. In comparison to TNF-α treated cells under non-perfused conditions, TNF-α stimulation under perfused conditions (i) did not affect cell survival but reduced apoptosis, (ii) did not affect oxygen consumption but reduced glucose consumption and lactate production as a measure of glycolysis, and (iii) reduced the expression of IL-6 and soluble amounts of IL-6 but not of TNF-α whereas soluble amounts of TNF-α were enhanced. Furthermore, TNF-α stimulation (iv) reduced the expression of matrix degrading enzymes but (v) enhanced anabolic chondrogenic matrix proteins on mRNA.

Conclusion: In a 3D model that mimics OA, FSS as a mechanical stimulus provides a metabolic “feel-good” niche that reduces chondrocyte apoptosis, metabolic activity, and matrix metalloproteinase expression, increases matrix protein expression and protects against TNF-α-mediated cartilage degradation.

Acknowledgements: This project is funded by Sanofi-Aventis Deutschland GmbH.

Disclosure of Interests: Duc Ha Do Nguyen: None declared, Christina Lubahn: None declared, Thomas Leeuwe Employee of: Thomas Leeuw is a Sanofi employee and may hold shares and/or stock options in the company., Frank Buttgeiret: None declared, Timo Gaber: None declared, Alexandra Damerau: None declared

DOI: 10.1136/annrheumdis-2022-eular.948

**POS0226**

**DEFICIENT CHAPERONE-MEDIATED AUTOPHagy CONTRIBUTES TO JOINT DAMAGE IN OSTEOARTHRITIS**

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Background: In Osteoarthritis (OA), defects in macroautophagy are evident and precede joint damage. Indeed, pharmacological activation of macroautophagy protects against joint damage and disease.

Objectives: Therefore, identifying hallmarks associated with specific autophagy subtypes could shed light to fundamental mechanisms of joint disease and facilitate the development of therapeutic strategies to prevent OA progression.

Methods: A gene expression analysis of 35 autophagy genes was performed from blood from a Prospective OA Cohort of A Coruña (PROCOAC) of non-OA (Age:61,44±1,16 years; BMI:25,25±5,02; Females, n=18) and knee OA subjects (Age:65,50±1,05 years; BMI:29,55±6,7; Females, n=18, OA grade III-IV) by using SYBR green array. The differential expression of candidate genes in blood (n=30/group) and knee cartilage (Non-OA, n=12; Knee OA donors, n=21) was confirmed by using TaqMan Technology. HSPA9A1, a chaperone mediated autophagy (CMA) protein, was selected and evaluated in human OA cartilage tissue (i.e. cartilage, meniscus, ACL and synovium) with different KL grades (0, 2 and 4, n=3/each KL grade) and in both spontaneous aging mice (2, 6, 12, 18, and 30 months old, n=3/each time) and surgically-induced OA mice (10 weeks after surgery; n=4/each) by immunohistochemistry. The functional consequences of HSPA9A1 deficiency on inflammation, oxidative stress, senescence and apoptosis were studied in human OA chondrocytes by gene and protein expression and flow cytometry. The potential contribution of CMA to chondrocyte homeostasis was studied by assessing the capacity of CMA to restore proteostasis upon macroautophagy deficiency by ATG5 knockdown. To study the therapeutic potential of targeting CMA, HSPA9A1 was overexpressed in human OA chondrocytes.

Results: 16 autophagy-related genes were significantly downregulated in knee OA subjects (p<0.05). Macroautophagy-related genes ATG16L2, ATG12, ATG4B and MAP1LC3B, were significantly downregulated (p<0.05). Interestingly, HSPA9A1 and HSPA9, CMA mediators involved in stress response and protein folding, were significantly downregulated (p<0.001). Confirmatory studies showed a downregulation of MAP1LC3B and HSPA9A1 in blood (p<0.001) and cartilage (p<0.05) from