9. Systemic sclerosis, myositis and related syndromes – etiology, pathogenesis and animal models

THU0324 AXONAL DYSFUNCTION IN CEREBRAL WHITE MATTER IN SYSTEMIC SCLEROSIS: A PROTON MAGNETIC RESONANCE SPECTROSCOPIC IMAGING (1H-MRSI) STUDY

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Background: Systemic sclerosis (SSc) is a diffuse connective tissue disease characterized by varying degrees of cutaneous and visceral fibrosis, presence of autoantibodies and vasculopathy. In addition, central nervous system (CNS) involvements are often observed [1].

Objectives: The aim of the present study was to investigate the presence of axonal dysfunction in systemic sclerosis (SSc) and to determine if clinical, laboratory and treatment features are associated with its occurrence.

Methods: In this longitudinal study we included 38 SSc patients (32 woman, mean age of 50.86, SD±11.66 years; range 31- 74) and 38 healthy volunteers (32 woman, mean age of 49.23, SD±12.03 years; range 26 - 77). All individuals were evaluated (neuropsychiatric evaluation and MRI) at study entry and after 12 months. Cognitive evaluation was performed using the Montreal Cognitive Assessment (MoCA), mood disorders were determined through Beck's Depression (BDI) and Beck's Anxiety Inventories (BAI). Individual with scores: MoCA ≤26, BDI ≥11 and BAI ≥7 were considered impaired. SSc patients were further assessed for clinical and laboratory SSc manifestations, disease activity (Valentini Activity Index), severity activity (Medsker Severity Index). We performed multi-voxel 1H-MRSI over the superior-posterior region of the corpus callosum. Our MRI/MRSI protocol consisted of: T1-weighted images; 2D pulse sequence (PRESS); excitation angle of 90°; Long TE: 144ms and TR: 2000ms; VOI (MRSI) size (mm) = (116 x 79 x 16) grid with 208 spectra. Scans were performed with a Philips 3.0T MRI scanner. We measured signals from N-acetyl-compounds (NAA), creatine (Cr), choline (Cho), glutamate (Glu), glutamine (Gln) and Glx (the sum of Glu and Gln) using TARQUIN software.

Statistics was performed according nature of the variable.

Results: We observed a significant reduction in NAA/Cr (mean value=1.72; SD=2.4) and Cho/Cr (mean value=2.4; SD=2.04) ratio in SSc when compared to controls (NAA/Cr mean value=1.85; SD=2.7; p = 0.36; Cho/Cr mean value=0.377; SD=0.169; p<0.001). Reduction in NAA/Cr ratio was associated with cognitive impairment (p = 0.017), presence of migraine (p = 0.001), current use of prednisone (p=0.010) and current use of methotrexate (p < 0.001). NAA/Cr ratio correlated with MOCA scores (r=0.4; p=0.015).

Follow up study showed a reduction in NAA/Cr values when compared to patients' baseline values (p = 0.0341).

Conclusion: Our results showed a significant reduction in NAA/Cr ratio in SSc patients associated with cognitive impairment and the use of some drugs (MTX and prednisone) during the treatment. Therefore, NAA/Cr ratios may be a useful biomarker in follow-up studies of SSc.

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Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.6011

THU0325 THE HMGB1/AGE-RAGE AXIS IN SYSTEMIC SCLEROSIS PATIENTS: A POTENTIAL ROLE IN ITS VASCULOPATHY?

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Background: Systemic sclerosis (SSc) is a progressive fibro-inflammatory autoimmune disease of which the pathogenetic pathways are incompletely understood. Advanced glycation endproducts (AGEs) are oxidative stress derived compounds with potential proinflammatory effects. Their exact role in fibrosis remains unknown. The receptor for AGEs is RAGE, which is also the receptor for high mobility group box 1 (HMGB1), a nuclear protein, which is proinflammatory when released from activated or apoptotic cells. We hypothesize that AGEs and HMGB1 may promote inflammation and profibrotic processes, presumably mediated by RAGE.

Objectives: To study the role of the HMGB1/AGE-RAGE axis in the pathogenesis of SSc.

Methods: Distribution of N-(carboxymethyl)lysine (CML) and N^ε-(5-hydro-5-methyl-4-imidazolone-2-yl)-ornithine (MG-H1) was assessed by immunohistochemistry in skin biopsies of 12 SSc patients [median age 56 years (IQR 52-61); 6 of affected, 6 of unaffected skin]. The intensity was assessed semi-quantitatively on endothelium and fibroblasts. In vitro experiments were performed on healthy human dermal fibroblasts, which were stimulated by HMGB1, AGE-BSA or TGF-β1 as control. Inflammatory and profibrotic markers were measured by ELISA and rt-PCR. Differentiation to myofibroblasts was assessed by staining of α-smooth muscle actin (α-SMA). In an additional clinical study, we included 20 SSc patients [51 years (44-58)] and 20 age- and sex-matched healthy controls [(HC) 52 years (45-62)]. Sera were obtained to determine CRP, ESR, HMGB1 and soluble RAGE (sRAGE) levels. AGE accumulation in skin was assessed as skin autofluorescence (SAF) by the AGE Reader.

Results: MG-H1 staining was more intense on all skin structures in SSc patients, compared to HC, while CML staining showed no differences. MG-H1 was more pronouncedly detected on endothelium and fibroblasts in affected compared to unaffected skin. In vitro stimulation of fibroblasts with AGE-BSA resulted in increased expression of IL-6, collagen-1α and connective tissue growth factor. Finally, HMGB1 and AGE-BSA induced myofibroblast differentiation and formation of SMA fibers (Fig. 1, 2). In regards to the clinical study CRP (SSc: median 1.8 mg/l (IQR 0.8-3.5), HC: 0.7 (0.4-1.8), p=0.04), ESR (SSc: 8.5 mm/h (5.3-15.5), HC: 5.0 (3.0-7.0), p=0.02), HMGB1 (SSc: 3.4 ng/ml (1.6-6.1), HC: 1.6 (0.8-2.8), p=0.03), sRAGE (SSc: 956.3 pg/ml (717.9-1670.0), HC: 684.9 (517.0-890.5), p=0.02) and SAF (SSc: 2.2 AU (1.8-2.5), HC: 1.8 (1.4-2.1), p=0.02) were significantly increased in SSc patients, compared to HC.

Conclusion: This is the first translational study that might indicate a prominent role of the HMGB1/AGE-RAGE axis in systemic sclerosis by promoting inflammation and fibrosis. Further studies investigating this pathway are ongoing.

Abstract THU0325 – Figure 1. Smooth muscle actin (α-SMA) expression by immunohistochemistry in stimulated and unstimulated human skin fibroblasts. Fibroblasts were treated with 0 (A), 1 (B), 10 (C) or 50 (D) ng/ml TGF-β1, 10 (E) or 100 (F) μg/ml AGE-BSA or 1 (G) or 10 (H) μg/ml HMGB1. All cells were treated for 24 hours. Detection was performed with 2 μg/ml anti α-SMA. Bar 100 μm.