Magnetic resonance imaging in murine spondyloarthropathy: a longitudinal study.

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Introduction: Spondyloarthropathy (SpA) refers to a cluster of interrelated chronic inflammatory diseases, of which typical members are ankylosing spondylitis, reactive arthritis, inflammatory bowel disease associated SpA and psoriatic arthritis. The axial disease affects the sacroiliac joints, the spine and the hips. Furthermore, there is an association with Crohn's inflammatory bowel disease. Due to their localisation, the sacroiliac joints, however, are very difficult to assess clinically.

To study murine SpA, we evaluated a model originally described by the group of G. Kollias, the TNF$^{\Delta ARE}$ mouse model (1). These mice are characterized by a dysregulated TNF (tumor necrosis factor) expression due to Cre-LoxP mediated excision of the AU-rich elements (adenosine-uracil multimers) in the TNF transcript, which results in the simultaneous occurrence of inflammatory bowel disease (Crohn´s disease) and peripheral and axial inflammation. Chronic TNF production induces mild swelling and distortion of paws, loss of grip, a hunched back, and diarrhoea. Because of the difficulty to assess sacroiliac joints, we set up an in vivo imaging procedure using magnetic resonance imaging to evaluate these joints in relation to disease duration.

Methods: Wild type (6) and TNF$^{\Delta ARE}$ (4) mice were submitted to an MRI study at age of 1, 2, 3, 5 and 7 months. MRI was performed on a 9.4 Tesla MR system (BRUKER, Ettlingen, Germany). Coronal T_1-weighted 2D images of the sacroiliac joints were acquired with a FLASH sequence: TE = 3.4 ms, TR=200 ms, FA= 40º, FOV=15 mm, image matrix (256 x 256), 16 slices, slice thickness = 0.5 mm T_2-weighted images were acquired with a RARE sequence with fat suppression: TE = 36 ms, TR=3000 ms, ETL=8, FOV= 19.2 mm, image matrix (256 x 192), 8 slices, slice thickness = 1 mm. To compare the T_2-weighted signal intensities of the ilium among animals and age, we calculated relative signal intensities of the ilium with respect to the mean signal intensity of the muscle tissue close to the ilium.

Results: During the course of the disease, the sacroiliac joints become gradually affected. Joint space narrowing can be very well appreciated on T_1-weighted images (fig. 1), eventually leading to joint bridging.

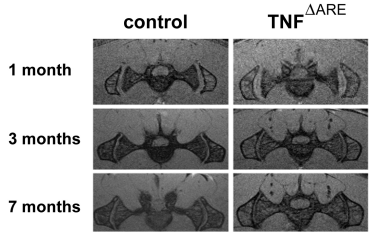

Figure 1: *T_1-weighted sections of sacroiliac joints of control TNF mice at the age of 1, 3 and 7 months.*

Furthermore, as compared to healthy controls, both sacrum and iliac bones remain very poorly mineralized until 7 months of age (fig. 2). A 2-way ANOVA demonstrated differences in relative T_2-weighted signal intensities – as a measure of mineralization –between the group of control and TNF mice and for the different ages of the mice.

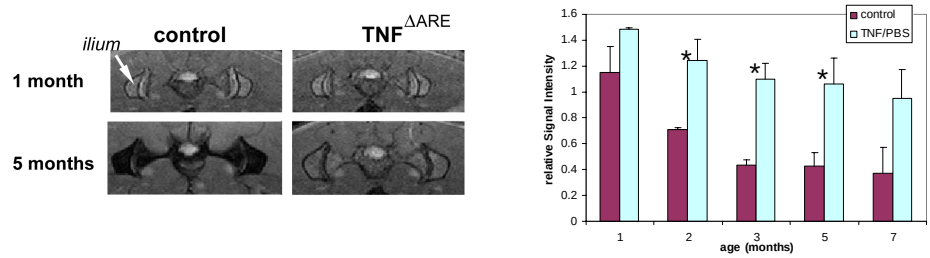

Figure 2*: Left: T_2-weighted sections of sacroiliac joints of control TNF mice at the age of 1 and 5 months, white arrow shows the ilium. Right: The graph gives the relative T_2-weighted signal intensities of the ilium with respect to a neighbouring muscle control region for control and TNF mice and for different age. (*) represents the age group for which a Student t-test demonstrated a difference of the relative signal intensities between the control and TNF mice ($p<0.05$).*

Conclusion: We conclude that in addition to an inflammatory syndrome strongly resembling SpA, chronic TNF exposure also has detrimental effects on normal bone mineralization. In summary, MRI imaging of sacroiliac joints is an important tool to monitor axial inflammation in preclinical models of SpA.

Reference:

1) Kontoyiannis D. et al. (1999). Immunity Vol. 10, 387–398 Impaired on-off regulation of TNF Biosynthesis in Mice Lacking TNF AU-Rich Elements: Implications for Joint and Gut-Associated Immunopathologies.