AB0151

EXPRESSION OF ANXIETY AND DEPRESSION IN PATIENTS WITH ANKYLOSING SPONDYLITE DEPENDING ON THE STATE OF THE AUTONOMIC NERVOUS SYSTEM AND INTENSITY OF THE PAIN SYNDROME

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Background: Chronic pain syndrome, immanent in the majority of immune-inflammatory processes, is one of the pathophysiological mechanisms of the development of emotional and affective disorders. It has been proven that high levels of "pro-inflammatory" mediators are predictors of depression, and increased anxiety leads to an imbalance in the autonomic nervous system (ANS). It is also known that the pain syndrome worsens the autonomic supply of the organism. However, this problem remains insufficiently studied today.

Objectives: To assess the severity of anxiety and depression in patients with ankylosing spondylite, depending on the state of the ANS and pain syndrome.

Methods: The study included 75 patients with ankylosing spondylitis (AS), who studied the frequency of anxiety-depressive disorders and their severity on the Spielberger anxiety and Hamilton depression scales. The autonomic status was investigated according to the methods "Wayne-patient" - WP, filled by the patient (more than 15 points - possible autonomic dysfunction (AD)) and "Wayne-doctor" - WD, filled by a doctor (more than 25 points - confirms the presence of signs of AD); we evaluated the indicators of heart rate variability (HRV) - mode (Mo), mode amplitude (AMo), autonomic equilibrium index (AEI), regulatory systems tension index (TI), the standard deviation of the normal RR intervals (SDNN), the square root of the mean squares of the difference between successive RR intervals (RMSSD) and the balance ratio of the activity of the sympathetic and parasympathetic divisions of the ANS (LF/HF). Pain syndrome and the patient's own health index (POH) were assessed by a visual analogue scale (VAS) by patients, and by a physician - by counting the number of painful joints (NPJ), index BASDAI and ASDAS indices.

Results: In 25.3% of patients with AS, a high situational anxiety was observed and in 36% of patients high personal anxiety (PA) was observed. Depressive disorders were found in 57 patients with AS (76%). The severity of pain in the joints and the spine influenced the increase in PA ($F = 2.75$, $p = 0.047$; $F = 3.54$, $p = 0.037$, respectively) and the level of depressive disorders ($F = 3.28$, $p = 0.03$; $F = 3.44$, $p = 0.047$, respectively), and the level of depression is also POH ($F = 3.49$, $p = 0.048$). 68% patients had an AD (according to WP and WD methods). They constituted the 1st group of observation, and the remaining 24 patients were included in the 2nd group. In group 1, signs of anxiety disorders were identified in 84.3% of cases, and in patients without AD in 45.8% of cases. Depressive disorders were observed in 94% patients with autonomic disorders (11 cases of psychotic, 37 - non-psychotic depression) and in 37.5% in patients without signs of AD - signs of non-psychotic depression.

In both groups, there was a decrease in SDNN and RMSSD in comparison with normative ones, which indicates an increase in sympathetic regulation. In the 1st group, there was a more significant increase in LF/HF (4.15 ± 0.64) and a decrease in SDNN (22.4 ± 5.6 ms) than in the 2nd (3.0 ± 0.86 ; 29.1 ± 8.4 ms), which indicates the connection between the strengthening of the sympathetic regulation link and the presence of signs of psycho-emotional disorders. The growth of AMo in the 1st group ($47.9 \pm 8.4\%$) reflects the degree of mobilizing influence of the sympathetic division and indicates an increase in the activation of the central contour and the growth of sympathetic regulation in patients with AS with AD.

Conclusion: Patients with AS have a high incidence of clinically significant anxiety and depression, which were affected by the intensity of the pain syndrome. The presence of autonomic imbalance and dysregulation of the sympathetic link of the ANS also contribute to the strengthening of psycho-emotional disorders in this category of patients.

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AB0152

IL-23 INDUCES OSTEOCLASTS TO EXPRESS PRO-OSTEOGENIC FACTORS RATHER THAN ANTI-OSTEOGENIC FACTORS

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Background: The formation of new bone or syndesmophytes is the dominant factor of the damage caused by AS, but the mechanisms responsible for syndesmophyte formation in AS have not been elucidated.

Objectives: To explore whether IL-23 indirectly facilitates new bone formation through osteoclasts in ankylosing spondylitis, here we analyzed whether IL-23 enhances the expression levels of osteogenic factors by osteoclasts.

Methods: Mouse bone marrow mononuclear cells were cultured in the presence of M-CSF (50ng/ml) and receptor activator of NF- κ B ligand (RANKL, 30ng/ml) to

induce osteoclast formation *in vitro*. The mRNA and protein expression levels of the osteogenesis-modulating factors, such as ephrin B2, sphingosine kinase 1 (SPHK1), bone morphogenetic protein 2 (BMP2), BMP6, Wnt10b, semaphorin 4D and HtrA1, were analyzed by quantitative real-time RT-PCR and Western blotting. **Results:** Mature osteoclasts were successfully induced from primary bone marrow mononuclear cells in the presence of both M-CSF and RANKL. Mature osteoclasts were identified by elevated expression levels of tartrate-resistant acid phosphatase (TRAP) and NFATc1, as well as positive TRAP staining with more than 3 nuclei. IL-23 increased the mRNA expression levels of pro-osteogenic ephrin B2, SPHK1 and BMP2 in osteoclasts to 2.1, 2.46 and 1.46 folds, respectively. The elevated protein levels of ephrin B2 and SPHK1 in IL-23-stimulated osteoclasts were also confirmed by Western blotting. IL-23 failed to enhance the expression levels of pro-osteogenic BMP6 and Wnt10b and showed no effects on the expression levels of anti-osteogenic semaphorin 4D and HtrA1 in osteoclasts. **Conclusion:** IL-23 induces osteoclasts to express pro-osteogenic factors rather than anti-osteogenic factors, suggesting IL-23 may indirectly promote the differentiation of osteoblasts through osteoclasts in ankylosing spondylitis.

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AB0153

CLINICAL SIGNIFICANCE OF MONOCYTE TO HEMOGLOBIN RATIO AND PLATELET TO ALBUMIN RATIO IN PATIENTS WITH AXIAL SPONDYLOARTHRITIS

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Background: Axial spondyloarthritis (axSpA) is a progressive, chronic, inflammatory skeletal disorder. Platelet to hemoglobin ratio (PHR) and platelet to albumin ratio (PAR) have been recommended as prognostic factor of cancer. However, none of study has focused on the clinical significance of PHR, PAR, neutrophil to hemoglobin ratio (NHR), neutrophil to albumin ratio (NAR), monocyte to hemoglobin ratio (MHR), monocyte to albumin ratio (MAR) for axSpA.

Objectives: The study aims to determine the clinical significance of NHR, NAR, MHR, MAR, PHR, PAR for axSpA.

Methods: A total of 198 axSpA patients and 48 healthy subjects were enrolled in the study retrospectively. Neutrophil, monocyte, platelet, hemoglobin, albumin, NHR, NAR, MHR, MAR, PHR, PAR, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) were collected. AxSpA patients were divided into remission group (BASDAI < 4) and active group (BASDAI $\geq$ 4). Relationships between the parameters and BASDAI were assessed by the Spearman's correlations analysis. Receiver operation characteristic (ROC) curves were used to discriminate axSpA patients from healthy subjects and active group from remission group.

Results: Neutrophil, monocyte, platelet, NHR, NAR, MHR, MAR, PHR, PAR, CRP, ESR in axSpA group were higher than those of control group, while albumin and hemoglobin were lower ($P < 0.05$). ROC curve results showed that the AUC value of MHR for axSpA were 0.808 (CI95%: 0.738-0.878), yielding a highest AUC value than other parameters. The optimal cutoff value of MHR for axSpA was 0.002447, with the Youden index of 0.498, sensitivity of 87.4% and specificity of 62.5%. The closely positive correlations were found between PAR and BASDAI ($r = 0.379$, $P < 0.001$). Besides, platelet, NAR, MAR, PHR, PAR, CRP, ESR in active group were higher than those of remission group, while albumin were lower ($P < 0.05$). ROC curve results showed that the AUC value of PAR for active group were 0.693 (CI95%: 0.610-0.775), yielding a highest AUC value than other parameters. The optimal cutoff value of PAR for active group was 5.967, with the Youden index of 0.354, sensitivity of 83.3% and specificity of 52.1%.

Figure 1 ROC curves were used to discriminate axSpA patients from healthy subjects(A) and active group from remission group(B).

Conclusion: MHR was elevated in axSpA patients with a highest diagnostic value. PAR was elevated in active axSpA patients, showing a significant correlation to the disease activity.

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AB0154 WNT-BETA CATENIN PATHWAY MAY BE UPREGULATED IN ANKYLOSING SPONDYLITIS

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Background: The Wnt- β -catenin pathway may play a critical role in new bone formation in ankylosing spondylitis. Wnt- β -catenin signaling depends primarily on the activity of glycogen synthase kinase-3 β (GSK3 β) that plays a key role in controlling β -catenin stability/degradation. It has been clearly established that phosphorylation of serine 9 in GSK3 β correlates with the inhibition of its kinase activity and stabilization of β -catenin. Dickkopf-1 (DKK1) and sclerostin (SOST) are both upstream inhibitors of the Wnt/ β -catenin pathway. Given that AS is associated with new bone formation we are interested in the molecular pathways that lead to this clinical phenotype

Objectives: The objective of our studies was to test the hypothesis that "alterations in the Wnt- β -catenin activity may be a contributing factor in the pathogenesis of AS"

Methods: 5 healthy donors and 12 patients (mean age 48 y.o., HLA-B27+ 70%) with AS based on New York classification criteria were enrolled. RNA was extracted from whole blood collected in PAX tubes following PreAnalytik kit protocol. Total mRNA was reverse transcribed using the high capacity cDNA Reverse Transcription Kit (Thermo Scientific) according to the manufacturer's instructions. TaqMan® Gene Expression Assays (IDT) were used to quantify mRNA levels of DKK1, SOST, and β -catenin. LightCycler480, and $\Delta\Delta C_T$ method were used to quantify the data (normalized to RPLP0(60S acidic ribosomal protein P0)). Protein lysates were prepared using NucleoSpin RNA/Protein kit (Takara) from PBMCs isolated from blood collected from the same 12 patients. Equal amounts of protein were loaded on 4–12% SDS gels and transferred to PVDF membranes. Membranes were blocked with 5% milk in TBST and probed at 4°C overnight with primary antibodies [rabbit anti-phosphoGSK3 β (Ser9) (1:500; Cell Signaling, #9336), rabbit anti-GSK3 β (1:1000; Cell Signaling, #9315), and mouse anti- β -actin (1:1000; Santa Cruz Biotechnologies, sc-47778)]. Appropriate HRP-conjugated secondary antibody was applied at room temperature for 1 hour. Immunoreactive protein bands were visualized using ECL (Pierce) and imaged with VisionWorks Image Acquisition and Analysis Software (Analytik Jena US, Upland, CA). β -actin was used as a loading control.

Results: Compared to healthy controls the mRNA levels of DKK1 and SOST were significantly lower in AS patients ($p < 0.001$), while the mRNA level of β -catenin was significantly higher in AS patients than in healthy controls ($p < 0.05$) (Fig 1).

Compared to healthy controls, there was a several fold increase in the phosphorylation of GSK3 β (Ser9) protein in the AS patient's sample.

Conclusion: These data indicate that altered Wnt- β -Catenin activity may be contributing to the new bone formation in AS patients and thereby contributing to the disease pathogenesis and can be targeted for therapeutic development.

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AB0155 INTESTINAL MICROBIAL SIGNATURE IN ANKYLOSING SPONDYLITIS

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Background: Intestinal microbiota analysis is a current subject because of its important role in the pathogenesis of various autoimmune diseases such as intestinal inflammatory diseases or spondyloarthritis.

Objectives: The objective of this paper was to perform a quantitative determination of the intestinal microbiota in patients with ankylosing spondylitis (AS) and to highlight the main characteristics of intestinal dysbiosis in these cases.

Methods: We conducted a case-control prospective study that included 28 patients with AS and 32 control cases (healthy individuals). Intestinal microbiota analysis was performed by real-time PCR (polymerase chain reaction) in faeces. Intestinal microbiota analysis focused on the following bacterial species: *Bacteroides*, *Bifidobacterium*, *Clostridium coccoides* (XIVa) (*C. Coccoides*), *Clostridium leptum* (IV) (*C. Leptum*), *Faecalibacterium prausnitzii* (*F. prausnitzii*), *Lactobacillus*, *Escherichia coli* (*E. coli*).

Results: Intestinal dysbiosis in AS patients was characterized by a significant bacterial decrease compared to the control arm. Some bacterial species showed a numerical growth: *Bacteroides*, *C. coccoides* and *C. leptum*, *F. prausnitzii*. In other bacterial groups there was a significant decrease: *Bifidobacterium*, *Lactobacillus* and *E. coli*. Statistically significant correlations were observed only for *Bifidobacterium*, significantly increased in the axial form of AS compared to the peripheral form ($p = 0.035$). Other bacterial groups were numerically elevated in the axial form of AS (except *Bacteroides*), without statistically significant differences. In all AS cases, a moderate disease activity was evidenced (mean BASDAI = 4.83, mean BASFI = 9.11). BASDAI score inversely correlated with the total bacteria group ($p = 0.010$, $r = -0.606$) - intestinal dysbiosis worsens as disease activity increases. Also, direct proportional correlations were highlighted between BASDAI and *F. prausnitzii* ($p = 0.000$, $r = 0.764$), respectively *Lactobacillus* ($p = 0.047$, $r = 0.488$). An increase in AS activity is associated with an increase in proinflammatory bacteria. BASFI score statistically correlated with the total bacterial count ($p = 0.000$, $r = -0.764$), *F. prausnitzii* ($p = 0.010$, $r = 0.606$), *Bifidobacterium* ($p = 0.016$, $r = 0.843$) and *E. coli* ($p = 0.016$, $r = 0.575$). An important decrease in the functionality of these patients correlates with a decrease in total bacterial diversity. Improvement of intestinal dysbiosis has been observed in patients on synthetic and biological immunosuppressive therapy compared to the control arm.

Conclusion: The study highlights the characteristics of intestinal dysbiosis in AS patients. There is a direct relationship between the composition of intestinal microbiota and the AS activity scores. Specific treatment for AS leads to a decrease in proinflammatory bacteria, improving gut dysbiosis.

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