ORIGINAL INVESTIGATIONS

Coxitis in early axial spondyloarthritis

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In Russia, coxitis is one of the most common extra-axial manifestations of ankylosing spondylitis (AS). However, many issues regarding its early diagnosis remain unresolved.
Objective: *to compare the clinical manifestations of coxitis with the data from an instrumental examination of CoRSAR cohort (Cohort of Early Axial Spondyloarthritis) patients.*
Patients and methods. *Examinations were made in 175 patients (mean age, 28.2±5.7 years) diagnosed as having axial spondyloarthritis (axSpA) with inflammatory back pain lasting up to 5 years, which occurred at the age of ⩽45 years. There was non-radiographic axSpA (nr-axSpA) in 69 patients and AS in 106 patients. 87% of patients were HLA-B27-positive. The median disease duration was 23.8 [1–60] months; BASDAI was 3.3±1.94. Regardless of complaints, all the patients underwent hip X-ray and ultrasound studies and 54 more patients had magnetic resonance imaging (MRI).*
Results and discussion. *The clinical signs of coxitis were present in 95 (54%) patients, of them 60% were diagnosed with AS and 40% had nr-axSpA. According to the numerical pain rating scale (NPRS), the median hip joint pain was 4 [3; 7]. Limited joint movement was observed in 6 (3.4%) patients. The level of hip joint pain correlated with BASDAI (r=0.53) and ASDAS (r=0.30). The ultrasound signs of coxitis were detected in 42 (24%) patients; of them 26 (62%) had the clinical manifestations of hip joint injury, and such changes were absent in 16 patients. The patients with ultrasound signs of coxitis were noted to have a higher disease activity; peripheral arthritis and enthesitis were more common. According to MRI, coxitis was diagnosed in 39 (72%) of the 54 examinees, while the disease was asymptomatic in 10%.*
Conclusion. *Different diagnostic methods used in patients with early axSpA could reveal coxitis in 33% of cases. The patients with coxitis show higher laboratory disease activity than those without hip joint injury. It is necessary to include MRI and ultrasound in the mandatory examination of patients with axSpA.*

Keywords: *early axial spondyloarthritis; ankylosing spondylitis; non-radiographic axial spondyloarthiritis; coxitis; ultrasonography; magnetic resonance imaging.*
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The axial spondylarthritis (axSpA) is a group of spondyloarthritides (SpA) that have common clinical, genetic and radiological features [1], which is divided into non-radiological axSpA (nr-axSpA) and ankylosing spondylitis (AS). In our earlier study, it was shown that the main difference between them is the presence or absence of radiologically detected sacroiliitis (SI) [2]. Given the multifactorial nature of axSpA, clinical polymorphism is considered to be its characteristic feature, which, in turn, implies not only a variety of clinical manifestations of the disease, but also varying severity and rate of development of structural and organ lesions. Accordingly, the clinical picture of axSpA can be represented by a wide range of manifestations – from low-symptom, practically not disturbing the patient, to extremely severe, leading to disability for several years.

Coxitis is known to be one of the manifestations of AS, which can quickly incapacitate a patient. According to domestic studies, damage to the hip joints (HJ) occurs in half of patients with AS [3]. With the exception of our two-year observation [4], there has been virtually no work on the study of coxitis in patients with early axSpA. It is still not known what factors cause the development of coxitis with axSpA, there is no generally accepted algorithm for diagnosing this condition, especially at an early stage. Previous studies have shown that coxitis in patients with AS develops on average 5P10 years after the onset of the disease, some patients already have irreversible changes in HJ at the time of diagnosis, and some patients do not develop coxitis [5].

The main method for diagnosing structural changes in HJ is radiological, with the help of which already irreversible changes in the joint are revealed. Recently, in the presence of clinical symptoms, ultrasound (US) and magnetic resonance imaging (MRI) have been increasingly used to confirm coxitis.

Despite recognition of the importance of the problem of coxitis, many unresolved issues remain regarding the definitions, classification, clinical and prognostic significance of HJ lesions in the case of axSpA.

The aim of the study was to compare clinical manifestations of coxitis with the data of instrumental examination in patients of the CoRSAr cohort (Cohort of the Early Axial SpondyloArthritis).

Patients and methods. The analysis included 175 patients with axSpA from the CoRSAr cohort with the duration of inflammatory back pain up to 5 years that occurred in patients aged I 45 years. Sixty nine (39%) patients met AS criteria (The Assessment of SpondyloArthritis international Society, ASAS, 2009), 106 patients (61%) – AS modified New York criteria (1984).

A special thematic map was filled out for each patient (demographic data, medical history, assessment of clinical manifestations of SPA, including lesions of the axial skeleton, peripheral joints, entheses, eyes, skin, and intestines). In all patients, CRP levels (highly sensitive method) and ESR, (Vestegren method) were determined, and every 6 months HJ ultrasound was performed according to the generally accepted method [6]. Assessment of disease activity and functional status was carried out in accordance with international and domestic recommendations [7, 8].

The diagnosis of coxitis was established on the basis of the following clinical signs: pain in the region of HJ at rest, with active and passive movements and / or restriction of movements in HJ. To assess the severity of pain in each HJ, a numerical rating scale (NCP, 0P10) was used, and any pain intensity was taken into account, including the minimum (NCP i1). All patients were examined to exclude enthesitis in the HJ area (large trochanters, sciatic tubercles, anteroposterior and anteroposterior iliac spine).

Ultrasound of HJ was performed on a MyLabTwice apparatus (ESAOTE, Italy, 13 MHz sensor). The presence of effusion in the joint cavity was considered corresponding to coxitis when the distance between the signals from the joint capsule to the inner part of the femoral neck (cervical-capsular distance (SCD) was > 7 mm [9].

X-ray of the pelvic bones was performed in accordance with previously published recommendations [10]. All HJ radiographs were evaluated independently by two experts – a rheumatologist and a radiologist. The BASRI-hip index (Bath Ankylosing Spondylitis Roentgenologic Index-hip) was used to determine the radiological severity of HJ lesion [11]. When analyzing the radiographs, the width of the joint space, the presence of bone growths along the edges of the articular surfaces, the state of the articular surfaces, and the shape of the femoral head were taken into account. X-ray transparency of bone tissue in the region of HJ (osteoporosis, osteosclerosis) was not recorded due to difficulties in objectification and the lack of an algorithm for describing these changes during radiography.

Fifty four patients underwent MRI of HJ in coronary and axial projections in T1 and STIR modes. The study was performed if a patient had ultrasound, radiological and / or clinical signs of coxitis. Given the lack of generally accepted methods for evaluating HJ MRI data, in the present work osteitis of the femoral head and / or acetabulum and synovitis were taken as active inflammatory changes in HJ. All tomograms were also analyzed by two independent experts – a radiologist and a rheumatologist. If the estimates did not coincide, the final analysis included their consolidated opinion.

Thus, **coxitis was taken**: *during physical examination*: pain during movement in the HJ and / or restriction of movements in the joint (internal and / or external rotation); with ultrasound: an increase in SCD > 7 mm or the presence of asymmetry > 1.5 mm between the joints; X-ray: BASRI-hip > 1; with MRI: synovitis; osteitis of the femoral head and / or acetabulum.

The clinical characteristics of patients with axSpA are presented in Table. 1. The average age of patients was 28.2 ± 5.7 years, the median duration of the disease at the time of examination was 23.8 [1–60] months. HLA-B27 antigen was present in the vast majority of patients. On average, disease activity according to BASDAI (Bath Ankylosing Disease Activity Index) was moderate, and according to the ASDAS index (CRP; Ankylosing Spondylitis Disease Activity Score) – high.

Statistical analysis was performed using the Statistica 12.0 computer program (StatSoft, USA).

Results. Clinical signs of coxitis were present in 95 (51%) of 175 patients, including 57 (54%) with AS and 38 (55%) with HP-AxSpA. Pain in HJ occurred in 55 (55%) men and 40 (52%) women. Movement restriction in HJ was detected in 6 (3%) patients. The median pain (according to NCP) in HJ was 4 [3; 7]: severe pain (> 4.0 for NCP) was observed in 36% of cases, and moderate pain in 64% (2 to 4 for NCP). An association was established between the level of pain in HJ and the clinical activity index of axSpA, such as BASDAI (r = 0.5) and ASDAS (CRP); r = 0.3, and the functional status of the patient; r = 0.53. At the same time, no relationship between the level of pain and SCD was found (r = 0.01).

In most patients, HJ pain occurred in the first year of the disease (43%): at the onset, in 30%; and 2P4 years after the first symptoms appeared, in 27%. In 47% of cases, inguinal pain was the reason for the initial visit to a doctor.

To assess the effect of pain in HJ on the activity, functional status, and other clinical manifestations of axSpA, all patients were divided into two groups depending on the presence or absence of this clinical sign (Table 2). Patients in both groups were comparable in age and duration of the disease.

Patients with complaints of inguinal pain had a higher disease activity according to BASDAI and ASDAS (CRP) and a greater decrease in BASFI functionality compared to those who did not have it. Also, peripheral arthritis was detected only in patients with clinical signs of coxitis, and enthesitis was 2 times more common in them, than in patients without clinical signs of HJ. Levels of ESR and CRP did not significantly differ.

X-ray analysis. In the vast majority of patients (n = 168, 96%), there were no radiological changes in HJ (BASRI-hip corresponded to stage 0 or stage I). Only 7 patients, mainly males (n = 6, 86%), showed marked structural disorders in HJ corresponding to BASRI-hip II P III. All patients with x-ray coxitis had bilateral II–IV stage. In 2 out of 7 patients, there were no clinical or ultrasound signs of coxitis.

Ultrasound HJ results. Ultrasound of HJ in 42 (24%) patients revealed an increase in SCD > 7, in 21 (50%) of them coxitis was bilateral in nature. In men, ultrasound signs of coxitis were more common than in women: 28% and 18%, respectively

Table **1**. *Clinical characteristics of patients with axSpA(n=175)*

Characteristic	Value
Men/women, n	98/77
Age, years, M±δ	28.2±5.7
Duration SpA, months, Me [min–max]	23.8 [1–60]
HLA-B27, n (%)	152 (87)
BASDAI, M±δ	3.3±1.94
BASFI, M±δ	1.75±1.9
ASDAS (SRP), M±δ	2.26 ±1.1
COE, mm/h, Me [min–max]	16.1 [1–80]
CRP, mg/L, Me [min–max]	16.8 [0.2–160]
Uveitis, n (%)	12 (7)
Arthritis of peripheral joints, n (%)	52 (30)
Enthesitis n (%)	70 (40)
Duration of HJ pain, months Me [min–max]	4.92 [0–60]

Note. BASFI - Bath Ankylosing Spondylitis Functional Index.

(p = 0.001). Given the quantitative differences between patients with clinical signs of coxitis and patients with ultrasound signs of HJ synovitis, an additional analysis was carried out to clarify the causes of this discrepancy. It turned out that effusion in HJ was found in 26 (27%) of 95 patients with clinical manifestations of coxitis. It should be noted, that in 16 patients in 56% of cases, SCD was > 8 mm, while they lacked both clinical and radiological signs of coxitis.

The data of the comparative analysis of patients with ultrasound signs of coxitis and without them are presented in Table. 3. Medians of age at the time of inclusion in the study did not differ in these groups.

Patients with ultrasound signs of coxitis had a higher laboratory activity of the disease, and they were more likely to experience peripheral arthritis and enthesitis. We hypothesized that a higher disease activity may not be associated with coxitis, but with the presence of peripheral arthritis.

To clarify the reasons for the high activity of the disease and the factors influencing it, three subgroups were formed from the general cohort of patients depending on the combination of ultrasound signs of coxitis and the presence of peripheral arthritis (Table 4). As can be seen from the data in Table. 4, the subgroups were comparable in age, duration of axSpA and ratio of men and women. Patients with a combination of ultrasound signs of coxitis and peripheral arthritis showed the highest disease activity compared to patients who had only ultrasound signs of coxitis or only arthritis of peripheral joints.

Results of MRI of HJ. Of 175 patients, HJ MRIs were performed in 54 (31%), and 39 (72%) showed the signs of coxitis. Most patients (35; 87%) had synovitis, 1 (3%) had osteitis, and 4 (10%) had a combination of osteitis and synovitis.

Signs of HJ lesion according to MRI were found in 27 (26%) men and 12 (16%) women. Most patients (72%) complained of pain in HJ, in the others the course of coxitis was asymptomatic. Patients with the presence or absence of coxitis according to MRI did not differ in the parameters presented in Table. 3.

Thus, in the CoRSAr cohort, clinical manifestations of coxitis were detected in 54% of patients, and ultrasound signs in 24%. Of the 54 patients who underwent MRI of HJ, coxitis was detected in 72% of cases. In general, the data obtained showed that in 57 patients the diagnosis of coxitis was established only clinically and was not confirmed by other imaging methods, while in the remaining 58 (33%) patients, coxitis was confirmed by at least one of the visualization methods. Note, that in most cases, coxitis was established by several methods and practically always was accompanied by a clinical picture characteristic of HJ damage (see Figure).

Discussion. A specific feature of our work is that it was performed on a cohort of patients with a short duration of the disease. It was found that at an early stage of axSpA, there is a high frequency of clinically detectable coxitis, which is due to several reasons. Firstly, due to the features of the collection of material, since we recorded any intensity of inguinal pain. Secondly,

Table **2**. *Characteristics of patients with axSpA with the presence or absence of clinical signs of coxitis*

Characteristic	Pain (n=95)	No pain (n=80)	R
Men/women, n	55/40	43/37	>0.05
HLA-B27, n (%)	74 (82)	78 (92)	>0.05
BASDAI, Me [25%, 75%;]	3.5 [2.3; 5.0]	2.6 [1.5; 4.2]	>0.05
BASFI, Me [25%, 75%;]	1.4 [0.6; 2.7]	0.7 [0.2; 2.1]	<0.05
ASDAS (CRP) Me [25%, 75%;]	2.5 [1.6; 3.2]	1.9 [1.3; 27]	>0.05
ESR, mm/h, Me [25%, 75%;]	10 [4; 23]	8 [5; 24]	>0.05
SRP, mg/L, Me [25%, 75%;]	3.5 [1.0; 22.6]	3.6 [0.9; 16]	>0.05
Uveitis (%)	5 (6)	7 (8)	>0.05
Arthritis of peripheral joints, n (%)	52 (56)	0 (0)	<0.05
Enthesitis, n (%)	42 (47)	26 (31)	<0.05
Patients with AS, n (%)	57 (60)	49 (62)	>0.05
Patients with nr-axSpA n (%)	38 (40)	31 (38)	>0.05

Table **3**. *Characteristics of patients with the presence and absence of ultrasound signs (US) of coxitis*

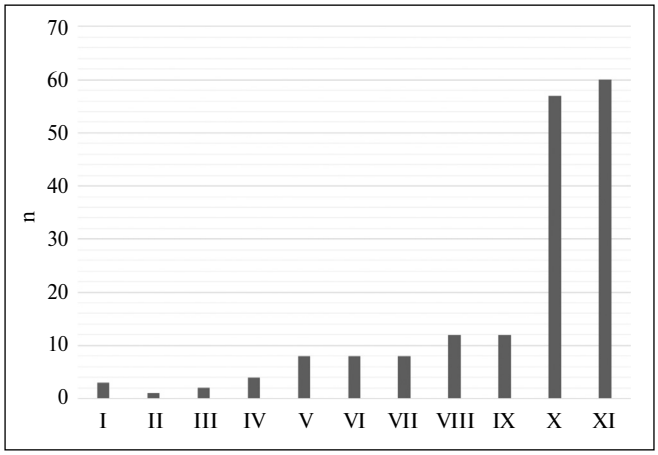
Characteristic	US coxitis (n=42)	No US coxitis (n=133)	R
Men/women, n	27/15	73/60	>0.05
Average age, years, Me [25%, 75%;]	30 [24; 34]	27.5 [25; 31]	>0.05
Duration of SpA, mo,Me [25%, 75%;]	18 [7; 25]	22 [10; 36]	>0.05
HLA-B27, n (%)	37 (88)	111 (83)	>0.05
BASDAI, Me [25%, 75%]	3.7 [2.0; 5.3]	2.8 [1.6; 4.2]	>0.05
ASDAS (CRP) Me [25%, 75%]	2.5 [1.9; 3.6]	2.0 [1.3; 2.7]	>0.05
ESR, mm/h, Me [25%, 75%;]	14 [5; 35]	8 [5; 19]	<0.05
SRP, mg/L, Me [25%, 75%;]	10 [2; 36.4]	3.6 [0.9; 14.5]	<0.05
BASFI, Me [25%, 75%;]	1.2 [0.4; 3.6]	1.0 [0.3; 2.2]	>0.05
Arthritis of peripheral joints, n (%)	21 (50)	31 (23)	<0.05
Enthesitis, n (%)	19 (45)	51 (38)	<0.05
Patients with AS, n (%)	28 (67)	78 (58)	>0.05
Patients with nr-axSpA n (%)	14 (33)	55 (42)	>0.05

Table **4**. *PatientsX characteristics depending on the presence or absence of peripheral arthritis and ultrasound signs (US) of coxitis*

Characteristic	Arthritis as US coxitis (+) (n=21)[1]	Arthritis+ as US (-) coxitis (n=31)[2]	Arthritis (-) as US (+) coxitis (n=21)[3]	P
Men/women, n	10/11	21/10	11/10	>0.05
Average age, years, Me [25%, 75%;]	30 [24; 34]	26.0 [25; 31]	29.0 [25; 32]	>0.05
Duration of SpA, mo, Me [25%, 75%;]	18 [7; 25]	22 [10; 36]	18 [8; 36]	>0.05
HLA-B27, n (%)	18 (88)	27 (90)	19 (90)	>0.05
BASDAI, Me [25%, 75%]	4.9 [1.9; 5.8]	5.2 [3.8;6.35]	3.2[2.0; 5.1]	>0.05
BASFI, Me [25%, 75%;]	2.0 [0.8; 4.1]	2.2 [0.7; 5.2]	1.7 [0.1; 3.5]	>0.05
ASDAS (CRP) Me [25%, 75%]	3.8 [2.0; 4.2]	3.2 [1.6; 3.8]	2.5 [1.6; 2.7]	<0.05*
ESR, mm/h, Me [25%, 75%;]	35 [15; 55]	25 [10; 35]	13 [5; 27]	<0.05*
SRP, mg/L, Me [25%, 75%;]	36.4 [4.6; 90.6]	30.3 [9.3; 50.3]	6.8 [1.2; 23.4]	<0.05*

although during a clinical examination we tried to exclude other causes of pain in the region of HJ, complete exclusion was probably not possible, and as a result, coxitis was not confirmed by instrumental methods in some patients with complaints of pain in the HJ region. The frequency of clinically detectable coxitis in our patients coincides with the data of other authors obtained previously in patients with AS [12].

In 38% of patients, HJ synovitis revealed by ultrasound was not accompanied by clinical symptoms, which can be explained either by a decrease in the threshold of pain sensitivity during anti-inflammatory therapy, or by the fact that an increase in SEC > 7 mm is their physiological norm. At the same time, in some cases, in the absence of clinical manifestations, coxitis was confirmed by the data of both ultrasound and MRI. This suggests that coxitis may be asymptomatic at the early stages of axSpA. The results obtained need further study. It is possible that excess fluid in the HJ cavity is not always a reliable confirmation of inflammation.



The distribution of patients depending on the method of coxitis detection. I – MRI; II – X-ray examination; III – clinical data – ultrasound – X-ray examination; IV – clinical data – ultrasound – X-ray examination – MRI; V – clinical data – ultrasound; VI – ultrasound – MRI; VII – ultrasound; VIII – clinical data – MRI; IX – clinical data – ultrasound and MRI; X – clinical data; XI – there is no pathology

It is interesting, that the radiological changes in HJ found in some patients were not accompanied by other signs of inflammation (clinical, ultrasound, MRI manifestations), which also requires further study.

The results of sonographic and radiological examinations showed that signs of coxitis are more often detected in men. These data are consistent with the results of previous studies [12]. In addition, the present study found that coxitis is often combined with inflammation of the peripheral joints, as well as with high laboratory and clinical activity of the disease. Probably, coxitis and peripheral arthritis aggravate the course of the disease and increase the activity of axSpA. In the previous studies [12P15], differences in activity (according to BASDAI) between patients with and without coxitis were not detected, which was also confirmed in our study. However, we did not observe differences in BASFI either, which is apparently due to the short duration of the disease in the analyzed cohort of patients.

Ultrasound has long been recognized as the best screening method for patients with effusion in the joint cavity. The lack of correlation between the results of ultrasound and MRI can be explained by their different capabilities in registering fluid in the HJ cavity. Apparently, with ultrasound diagnostics of coxitis in patients with AS, the norm of SCD should be increased.

Findings. Thus, the results of our work confirm the opinion of foreign and domestic researchers that coxitis is one of the significant factors affecting the prognosis of the disease even at an early stage. The data obtained allow us to recommend ultrasound and MRI for early diagnosis of coxitis in patients with axSpA. However, further studies are required to compare ultrasound and MRI signs in such patients in order to determine the significance of each method in the early diagnosis of coxitis, as well as its monitoring.

Early detection of coxitis in patients with axSpA can contribute to the timely correction of anti-inflammatory therapy, even in the absence of high disease activity, which will prevent structural changes in HJ.

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