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## **DISTURBANCE OF THE MUSCOLOSKELETAL SYSTEM IN JUVENILE ANKYLOSING SPONDYLITIS AND DISEASE DEVELOPED IN THE ADULTHOOD (INVOLVEMENT OF SPINE AND SACROILIAC JOINTS)**

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**Abstract.** *Disturbance of the musculoskeletal system in juvenile ankylosing spondylitis and disease developed in the adulthood (involvement of spine and sacroiliac joints). Yehudina Ye.D., Syniachenko O.V., Polesova T.R., Chernyshova O.E., Yermolaeva M.V. Background. Two forms of ankylosing spondylitis (AS) are distinguished: juvenile and adult, depending on debut age of the disease. The diagnosis of juvenile AS (JAS) is one of the most urgent problems in a pediatric rheumatology. The peculiarities of AS course that onsets in childhood and adulthood are manifested by differences in the nature of a spinal column disturbance. At the same time, the evolution of JAS in adulthood remains unexplored. The goals and objectives of research: to study clinical and X-ray symptoms of spondylopathy and sacroiliitis course, to assess their characteristics in the disease that onset in childhood and adulthood. Material and methods. 217 patients with AS (193 men and 24 women) with an average age of 38 years were examined. The fast-progressing course of the disease was detected in 21% of cases, moderate and high degree of activity – in 79% of cases, the II-III stage in 82%, and polyarthritis – in 65%. JAS was detected in 16% of cases (all boys), among them the third stage occurred twice more likely than among the other patients. Results. The clinical and radiologic signs of spondylopathy and sacroiliitis are observed in 95% and 97% of the total number of AS cases, respectively, among all patients with JAS lumbago was detected 4,3 times more frequently, sciatic muscles hypotrophy – 7,8 times, "the string symptom" - 2,9 times", the calcification of the spinal cord - 2,3 times, whereas the prevalence of spinal column injury, the severity of cervico-spondylopathy and sacroiliitis among patients with the disease debut in the adulthood is significantly greater, and the involvement in the process of the lumbar and thoracic spine are detected correspondingly twice as often and by 19%, occurrence of dorsalgia is 4 times as often, the limitation of body lateral bendover by 59%, while there are ambiguous dispersion-correlation links with extraarticular (systemic) manifestations of the disease, and the high prevalence of a peripheral articular syndrome regarding spondylopathy in JAS is a negative prognosis sign, and for the remaining patients there are indices of the Lansbury index and the index of arthropathy progression. Conclusion: the onset of AS in adulthood is a risk factor for the severe course of spondylopathy.*

**Реферат.** *Поражение опорно-двигательного аппарата при ювенильном анкилозирующем спондилите и заболевании, начавшемся во взрослом возрасте (вовлечение позвоночника и крестцово-подвздошных сочленений). Егудина Е.Д., Синяченко О.В., Полесова Т.Р., Чернышева О.Е., Ермолаева М.В. Актуальность проблемы. Выделяют две формы анкилозирующего спондилита (АС) – детскую и взрослую, в зависимости от возраста дебюта заболевания. Проблема диагностики ювенильного АС (ЮАС) относится к наиболее актуальным в педиатрической ревматологии. Особенности течения АС, начавшегося в детском и взрослом возрасте, проявляются различиями в характере поражения позвоночного столба. При этом эволюция ЮАС во взрослом возрасте остается неизученной. Цель и задачи исследования: изучить у больных АС клико-рентгенологические признаки течения спондилопатии и сакроилеита, оценить их особенности при*

заболевании, начавшемся в детском и взрослом возрасте. *Материал и методы.* Обследованы 217 больных АС (193 мужчины и 24 женщины) со средним возрастом 38 лет. Быстропрогрессирующее течение констатировано в 21% наблюдений, умеренная и высокая степень активности – в 79%, II-III стадия – в 82%, полиартрит – в 65%. ЮАС отмечен в 16% случаев (все мальчики), у которых III стадия имела место вдвое чаще, чем у остальных пациентов. *Результаты.* Клинико-рентгенологические признаки спондилопатии и сакроилеита наблюдаются соответственно у 95% и 97% от общего числа случаев АС, при этом у всех больных ЮАС, у которых в 4,3 раза чаще выявляются ломбаго, в 7,8 раза гипотрофия седалищных мышц, в 2,9 раза «симптом тетивы», в 2,3 раза кальцификация спинальных связок, тогда как распространенность поражения позвоночника, тяжесть цервикоспондилопатии и сакроилеита у пациентов с дебютом заболевания во взрослом возрасте достоверно большие, а вовлечение в процесс поясничного и грудного отделов позвоночника отмечается соответственно чаще вдвое и на 19%, появление дорсалгий – в 4 раза, ограничение боковых наклонов туловища – на 59%, при этом существуют неоднозначные дисперсионно-корреляционные связи с экстраартикулярными (системными) проявлениями болезни, а прогнознегативным признаком в отношении спондилопатии при ЮАС является большая распространенность периферического суставного синдрома, а у остальных больных – показатели индекса Лансбури и индекса прогрессирования артропатии. *Выводы:* начало АС во взрослом возрасте является фактором риска тяжелого течения спондилопатии.

**Background.** The prevalence of ankylosing spondylitis (AS) reaches 0.3% among the population [12, 16]. The modern concept divides this disease by the predominantly lesion of either the peripheral joints or the axial skeleton [3, 13, 14]. Meanwhile, two forms of AS are identified - juvenile (JAC) and adult (AAC), depending on the age of the disease debut [7, 9].

There are features of AS course that began in childhood and adulthood [2, 5, 14], which, first of all, is manifested by the differences in the nature of the spinal column lesion [1, 6]. At the same time there is a definite evolution of clinical manifestations of JAS in adult patients [8]. According to the literature, severe spine changes are rare in JAS [9], and involvement of the lumbar spine in the process, allegedly, is little typical for such patients [4, 6]. A. Adrovic et al. [10] attributed the presence of asymptomatic sacroileitis and the absence of spondylopathy in the debut of JAS like the distinctive clinical signs in the contrast to AAC. It should be noted that the problem of clarifying the nature of spondylitis and sacroiliitis in the early stages of JAS is among the most relevant in pediatric rheumatology [11, 15].

The purpose and objectives of the study: to study the clinical and radiological signs of the spondylopathy and sacroiliitis course in patients with AS, to evaluate their characteristics in the disease that began in childhood and adulthood.

#### **MATERIAL AND METHODS**

217 AS patients aged 16 to 57 years old (an average of  $37,7 \pm 0,64$  years) were under observation, 88,9% of men and 11,1% of women among them. The disease duration averaged  $10,5 \pm 0,39$  years. I degree of AS activity was established in 21,2% of cases, II – in 56,7% and III – in 22,1%, I stage was noted in 18,4% of the surveyed patients, II – in 50,7% and III – in 30,9%. Slowly progressive disease course occurred in 79,3% of cases, fast-

progressing – in 20,7%. The so-called "central form" of AS was diagnosed in 33,6% of cases, "rhizomelic" – in 2,8%, "peripheral" – in 5,1%, "undifferentiated" – 58,5%. Ophthalmopathy (uveitis), nervous system damage and visceral changes are established in  $\frac{3}{4}$  of the patients' number.

Peripheral arthritis was determined in 66,4% of the patients number. The prevalence of articular syndrome (number of painful joints - NPJ) was  $5,4 \pm 0,25$  r.u., its activity (DAS) –  $4,0 \pm 0,10$  r.u., Lansbury index (LI) –  $117,1 \pm 3,89$  points, progression of arthritis index (PAI) –  $1,3 \pm 0,15$  r.u. In the X-ray, sonography and densitometry studies, narrowing of the joint space was found in 38,7% of cases, subchondral sclerosis – in 12,9%, osteocystis – in 25,4%, epiphyseal osteoporosis - in 22,1%, systemic osteoporosis – in 51,2%, usuras of bone surface – in 10,6%, intraarticular calcifications – in 11,5%, changes in the horns of the knee joints menisci – in 18,0%, Baker's cysts – 6,0%, Shtaydie's bodies – 3,7%, chondromous bodies – 9,2%, Goff's bodies – 1,4%. The Barnett-Nordin meta-carpal index was  $0,43 \pm 0,004$  r.u., the bone mineral density index was  $-1,49 \pm 0,055$  SD. Enthesopathies were noted in 38,7% of the surveyed, tenosynovitis – in 28,6%.

All patients were divided into two groups: the first (main) amounted to 35 (16.1%) patients (all males) with onset of the disease under the age of 18 (JAS), and the others 182 (83.9%), with AAS were included in the 2nd (control) group. The age of the main group representatives in the disease debut was  $14,3 \pm 0,52$  years, and at the time of the examination –  $24,9 \pm 0,83$  years, while in the control group it was  $29,6 \pm 0,45$  years and  $40,2 \pm 0,58$  years respectively. The duration of the disease in the 1st and 2nd groups did not differ. Both groups were approximately equal in the disease degree activity, but fast progressing course of the disease in AAS was 2,7 times more common.

Patients have undergone X-ray ("Multix-Compact-Siemens", Germany) and ultrasound ("Envisor-Philips", Netherlands and "ATL3500-Siemens", Germany) studies of peripheral joints, sacroiliac joints and spine, dual-energy X-ray absorptiometry of the proximal femur ("Somazom-Emotion-6-Siemens", Germany) and magnetic resonance ("Gygoscan-Intera-Philips", the Netherlands) tomography of spondilopathy and sacroiliitis.

The serum levels of antibodies to cyclic citrullinated peptide (aCCP), the concentration of interleukin (IL) 1 $\beta$  and tumor necrosis factor (TNF) were studied using the enzyme immunoassay (PR2100 Sanofi diagnostic pasteur, France), and the immuno-biochemical analyzer "Olympus-AU-640" (Japan), concentrations of C-reactive protein (CRP), fibrinogen (FG), circulating immune complexes (CIC), immunoglobulins (Ig) A, G and M were determined in blood serum. The aCCP values in serum of the examined AS patients were 22,2 $\pm$ 8,41 $\pm$ 0,57 U/ml, CRP – 12,0 $\pm$ 5,89 $\pm$ 0,40 mg/l, FG – 7,4 $\pm$ 2,99 $\pm$ 0,20 g/l, IgA – 2,3 $\pm$ 0,58 $\pm$ 0,04 mmol/L, IgG – 15,7 $\pm$ 3,23 $\pm$ 0,22 mmol/l, IgM – 2,0 $\pm$ 0,62 $\pm$ 0,04 mmol/l, CIC – 104,5 $\pm$ 61,08 $\pm$ 4,15 r.u., IL1 $\beta$  – 88,5 $\pm$ 100,17 $\pm$ 6,80 pg/ml, TNF – 153,5 $\pm$ 220,12 $\pm$ 14,94 pg/ml.

Statistical analysis of the research results was carried out by computer variations, nonparametric, correlation, regression, one- (ANOVA) and multivariate (ANOVA / MANOVA) variance analysis (Microsoft Excel and Statistica-Stat-Soft, USA). The mean values (M), their standard deviations (SD) and standard errors (m), Pearson parametric correlation coefficients (r) and nonparametric Kendall ( $\tau$ ), Brown-Forsythe dispersion criteria (BF), Wilcoxon-Rao (WR), the multiple regression (R), Student (t) and McNamara-Fisher ( $\chi^2$ ), the reliability of statistical parameters (p).

## RESULTS AND DISCUSSION

Sacroiliitis was determined in all patients with AS, and signs of spondylopathy - in 94,9% of them. It should be noted that JAS and AAS differed a little from each other in spinal cord lesions, correspondingly being 100,0% and 94,0% of cases. This also referred to the severity of spondylopathy, which indices were 0,69 $\pm$ 0,084 points and 0,83 $\pm$ 0,041 points respectively in the 1st and 2nd groups. In the case of JAS, changes in the cervical spine ( $\chi^2=6,83$ , p=0,009) were more frequent by 33%, while in AAS, changes in lumbar region were twice as often ( $\chi^2=33,33$ , p<0,001) and thoracic spine – by 19% ( $\chi^2=5,60$ , p=0,018), whereas in the sacroileitis incidence, both groups did not differ.

Vertebralgia was noted in 88,5% of the patients with AS, thoracalgia – in 54,8%, dorsalgia – in

50,2%, pelvialgia – in 43,3%, back muscle hypotrophy – in 36,4%, restriction of the trunk lateral bendover – in 31,8%, vertebrobasilar insufficiency – in 30,9%, "petitioner's pose" – in 13,4%, soreness of the vertebrae spinous processes – in 10,1%, "string symptom" and discoid of the back – in 7,8%, lumbago – in 5,1%, sciatic muscles hypotrophy – in 4,6%. In the patients with JAS, dorsalgia was observed 4 times less frequent ( $\chi^2=21,57$ , p<0,001) and the restriction of the trunk lateral bendover – by 59% ( $\chi^2=5,90$ , p=0,015), but lumbago was found 4.3 times more often ( $\chi^2=7,37$ , p=0,007), sciatic muscles hypotrophy – 7.8 times ( $\chi^2=14,92$ , p<0,001) and "bowstrings symptom" – 2.9 times ( $\chi^2=5,01$ , p=0,025), which is reflected in Fig. 1-2.

Inflammatory, dishemic, mechanical and dysfunction character of painful spondylogenous syndromewas was established in 50,2%, 24,9%, 3,7% and 21,2%, respectively, of all patients with AS. The main and control groups differed a little from each other by the integral nature of pain, and also by the nature of vertebralgia.

Syndesmophytes were found in 89,9% of cases, spondylodyscitis – in 91,7%, narrowing of the facet joint fissure – in 83,0%, calcification of spinal ligamentum - in 13,4%, ossification of intervertebral discs – in 30,9%, ankylosis of facet joints - in 22,6%, which is represented in Fig. 3. It has been established that only calcification of spinal ligaments in JAS occurred 2,3 times more often than with AAS ( $\chi^2=5,50$ , p=0,019). The average severity of the cervical spine and sacroiliac joint lesion in patients with JAS was less by 25% of points (t=6,18, p <0,001) and 17% points (t=2,35, p=0,020), respectively.

According to Brown-Forsythe dispersion analysis, in JAS patients, the severity of spondylopathy is affected by seropositivity in aCCP (BF=5,08, p=0,012) and the prevalence of peripheral articular syndrome (BF=4,77, p=0,015), and in the control group – by character of the disease course (BF=6,85, p=0,001), the presence of tendovaginitis (BF=4,03, p=0,020), osteoporosis (BF=6,62, p=0,002), uveitis (BF=9,71, p<0,001) and peripheral neuropathy (BF=3,14, p=0,046), LI parameters (BF=3,17, p=0,045) and PAI (BF=3,10, p=0,048). In both JAS and AAS, the severity of spondylopathy rises proportionally to the increase in the patients' age and the disease duration, which is demonstrated by Pearson's correlation analysis (r=+0,405, p=0,018 and r=+0,378, p<0,001; r=+0,435, p=0,010 and r=+0,229, p<0,001). It should be noted that in the main group there is a direct correlation between the degree of spinal cord lesion and the NPJ index (r=+0,659, p<0,001), and in the control group – LI (r=+0,237, p=0,003). Taking into account the

performed dispersion-correlation analysis, it can be assumed that the risk factors for severe spondylopathy

in JAS is NPJ>10 r.u., and for AAS, LI>170 points (>M+SD of the corresponding groups of patients).

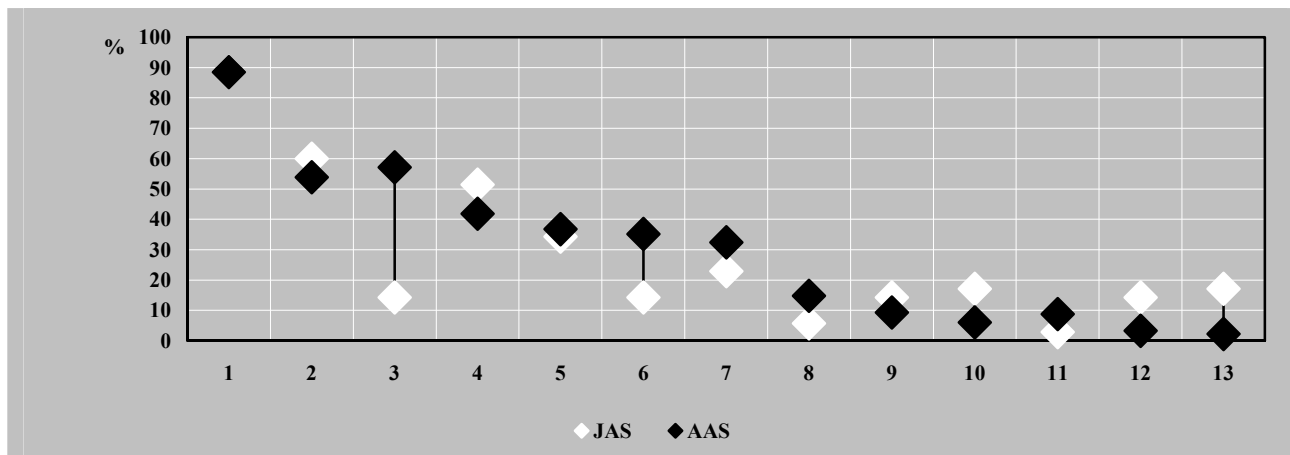
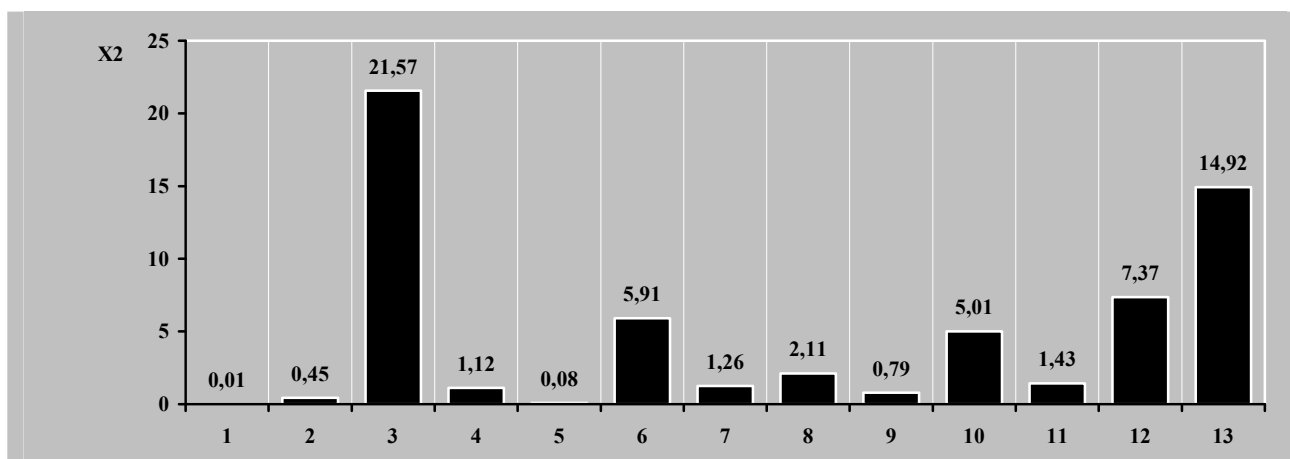


Fig. 1. Frequency of separate clinical signs in patients with JAS and AAS



1 - vertebralgia, 2 - thoracalgia, 3 - dorsalgia, 4 - pelvialgia, 5 - back rectus muscles hypotrophy, 6 - restriction of the trunk lateral bendover, 7 - vertebrobasilar insufficiency, 8 - "pose of the petitioner", 9 - soreness of the vertebrae spinous processes, 10 - "symptom of the bowstring", 11 - discoid of the back, 12 - lumbago, 13 - sciatic muscles hypotrophy

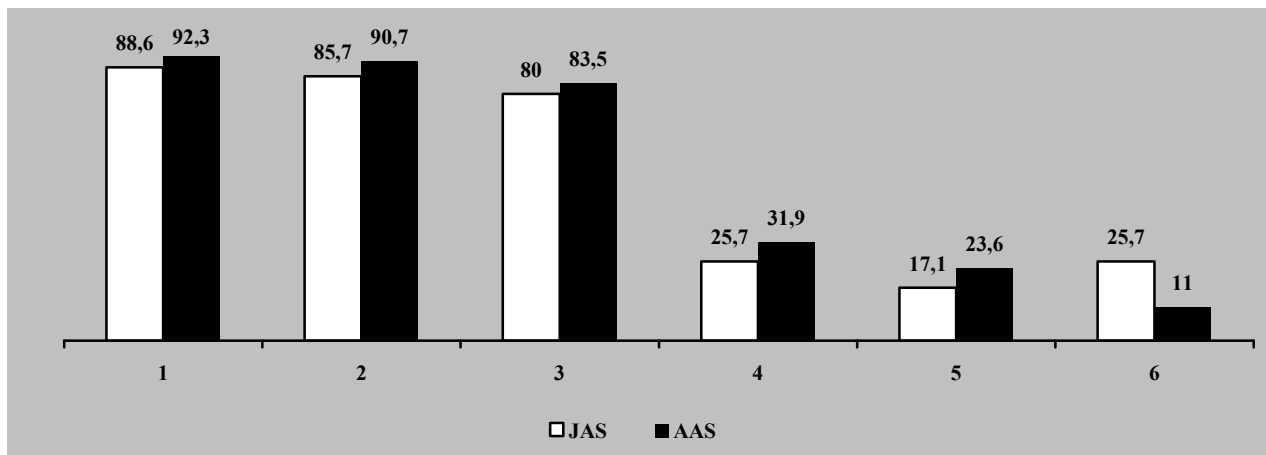
Fig. 2. Differences in patients with JAS and AAS

The presence of coxitis (BF=3,43, p=0,045) exerts a dispersion influence on severity of the spine injury in the main group patients, and involvement in the pathological process of the metatarsophalangeal joints (BF=3,76, p=0,025) – in the control group. Among all patients with AS, the degree of spondylopathy depends on the aCCP parameters (BF=25,79, p<0,001), FG (BF=3,31, p=0,039) and CIC (BF=3,84, p=0,023).

Attention was paid to Kendall's contradictory correlation relations between the severity of the spine lesion and some immunoinflammatory indicators of blood serum. So, if there are direct relations with the levels of aCCP ( $\tau=+0,387$ , p=0,022) and IgM ( $\tau=+0,366$ , p=0,030) in JAS, then CRP concentrations ( $\tau=+0,178$ , p=0,016), IgG ( $\tau=+0,208$ , p=0,005) and IL1 ( $\tau=+0,148$ , p=0,048) – in AAS.

It must be emphasized, as Wilcoxon-Rao multi-factor analysis demonstrated, the severity of spondylopathy has a significant influence (p<0.001) on other integral signs of the disease both in the main (WR=8,06) and control (WR=5,21) groups, and there are direct regression relations with the severity of immune-inflammatory disorders (R=+1,96, p=0,045 and R=+7,60, p<0,001, respectively).

In JAS, direct Kendall correlations between separate parameters of spine and peripheral joint lesions are established, in particular, the ratios of "syndesmophytes ↔ subchondral sclerosis" ( $\tau=+0,240$ , p=0,042), "spinal cord calcification ↔ arthrocalcinates" ( $\tau=+0,494$ , p<0,001), "narrowing of the facet joint fissure ↔ chondromous intra-articular bodies" ( $\tau=+0,251$ , p=0,035), "ossification of the intervertebral disks ↔ osteocystosis" ( $\tau=+0,359$ , p=0,002).



1 - spondylodiscitis, 2 - syndesmophytes, 3 - narrowing of the arcuate articulations, 4 - ossification of the intervertebral disks, 5 - ankylosis of the facet joints, 6 - calcification of the spinal cord

Fig. 3. The frequency of separate signs of spondylopathy in patients with JAS and AAS (%)

### CONCLUSIONS

1. Clinical and radiologic signs of spondylopathy and sacroiliitis are observed in 95% and 97% of the total number of AS patients, respectively, while in all patients with JAS

2. Lumbago is detected 4,3 times more often in JAS than in cases of AAS, hypotrophy of sciatic muscles – 7,8 times, "symptom of the bowstring" – 2,9 times, calcification of spinal ligaments – 2,3 times, while the prevalence of spine lesions, severity of cervico-spondylopathy and sacroiliitis are significantly greater in patients with debut of the disease in adulthood.

3. Involvement of the lumbar and thoracic spine in the process in patients with AAS is correspondingly more often by 2 times and by 19%, the appearance of dorsalgia – by 4 times, the restriction of the trunk lateral bendover – by 59%, while there are

controversal dispersion-correlation links with extra-articular (systemic) manifestations of the disease.

4. Negative prognosis sign of spondylopathy in JAS is the high prevalence of peripheral articular syndrome, and in AAS - LI and PAI indices.

5. In the future it will be useful to predict the course of spine and sacroiliac joint lesions in AS patients with the disease onset in childhood and adulthood for subsequent timely rehabilitation activities, and the assessment of spondylopathy and sacroiliitis components nature may have practical importance as risk factors for separate extraarticular signs of the disease.

**Conflict of interest.** The authors declare that there is no conflict of interest, while the authors have not received financial support for research from individuals and organizations, fees and other forms of rewards.

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