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Pauciarticular juvenile arthritis with ANF-associated uveitis: clinical observation of a family case (mother and daughter) with ankylosing spondylitis in outcome in the mother

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Article received: 19.11.2013. Accepted for publication: 14.01.2014.

Pauciarticular juvenile arthritis associated with antinuclear factor and uveitis with onset at an early age has a special place in the structure of juvenile arthrites. This variant of arthritis is characterized by unpredictability of nosological outcomes and the prognosis is often associated with unfavorable uveitis course. Joint syndrome is characterized by frequent dactylites, which are usually associated with psoriatic arthritis. The article presents clinical observation of a family case (mother and daughter) of juvenile arthritis with onset at an early age, eye lesion, homogenous clinical manifestations in the onset and manifestation of severe ankylosing spondylitis in the mother 25 years into the disease. Both patients started undergoing adalimumab therapy at the same time and very effectively. Clinical observation illustrates the need in timely prescription of a pathogenetically substantiated genetically engineered biological therapy in order to prevent incapacitation of patients with juvenile arthritis regarding condition of joints and organ of vision.

Key words: pauciarticular juvenile arthritis, psoriatic arthritis, uveitis, genetically engineered biological therapy, children.

Pauciarticular (oligoarticular) juvenile arthritis (JA) is the most frequent clinical variant of JA detected, according to various authors, in 27-74% of cases [1-6]. Most foreign trials [4, 6-8] indicate favorable course of this clinical variant, though this cannot be extrapolated to a certain patient's disease prognosis. Exceptional heterogeneity of this JA category characterized not only by a small number (up to 5) of affected joints in the first 6 months of the disease, but also by a range of common features (such as age of onset (it most often occurs in children under 6 years of age; morbidity peak – 1-2 years of age), sex (girls develop this disease considerably more often than boys (6:1)), high (up to 70-80%) rate of positive antinuclear factor (ANF) and, accordingly, high risk of uveitis development), is obvious. Unlike acute and painful uveites, which are specific manifestations of enthesitis-associated arthrites and ankylosing spondylitis, uveitis development in this case is characteristically asymptomatic (or oligosymptomatic).

Oligoarticular variant is divided into 2 subtypes – persistent and extended – according to the 1997 ILAR (International League of Associations for Rheumatology) international classification of juvenile idiopathic arthritis (JIA) [5] mostly for convenience purposes. Meta-analysis of a large number of trials by A. Ravelli [4] revealed that both subtypes are basically one disease; however, a more extended joint lesion involving joints of upper extremities and high erythrocyte sedimentation rate (ESR) considerable aggravate prognosis. Quite a large amount of scientific data indicating reasonability of considering ANF-positive JA patients a special subtype have been accumulated [4, 9, 10]. In the same review, A. Ravelli [4] notes that ANF-positive patients of both oligoarticular JIA subtypes appeared to be homogenous in sex, age, asymmetrical joint lesion and anterior uveitis rate. Moreover, there are some patients with a different JIA variant – seronegative (rheumatoid factor) polyarticular arthritis – who feature the same clinical manifestations. Many authors [11-13] note commonality of clinical presentation and demographic characteristics of the given clinical variant and psoriatic arthritis, including such common feature as dactylites.

Thus, regardless of quantitative characteristics of articular syndrome, we may highlight a range of key symptoms allowing singling out female JA patients with early age of onset, persistent ANF and extremely high risk of uveitis development as a special category. The fact that all characteristics of this clinical variant (sex of patients, age of onset, oligosymptomatic ophthalmic manifestations and low rate of antigen HLA-B27 carriage) allow considering it an antipode of enthesitis-associated arthrites despite formal similarity in terms of the number of affected joints and occurrence of uveitis is emphasized throughout the pediatric literature. Not a single competent specialist in this area has discussed the possibility of labeling the given variant as a spondyloarthritis [4, 14, 15]. Among all JA patients, patients with this clinical variant are characterized by unpredictability of functional and nosological outcome. It is commonly accepted as virtually the only JA subtype without an equivalent in adults. The accessible literature features no descriptions of a similar set of disease symptoms developing in adults; there are no unambiguous data on nosological outcomes of this variant of JA or convincing examples of ankylosing spondylitis development in adults as well.

We would like to bring to your attention our clinical observation of a family JA case (onset in the mother and her small daughter) with eye lesion.

Child K.K., born 02.03.2009, has been under observation at the Institute since 2012. Unremarkable early anamnesis: daughter of the second pregnancy without abnormalities, second-born child (caesarean section). Birth weight -2,870 g, height -49 cm, Apgar score -8-9. Breast feeding -1 week. No delay in neuropsychic development. Prophylactic immunization - according to age. Anamnesis vitae: acute respiratory viral infections (ARVI), acute gastroenteritis, allergic dermatitis.

Anamnesis morbi: onset in February 2011 (age of onset – 1 year 11 months) – pain and swelling in the right knee joint region, limping. Hospitalized to the inpatient hospital of one of the specialized federal centers, where arthrites of right knee joint and right wrist joint, dactylites of the third hand digits and moderate laboratory activity were revealed. Diagnosis - "Juvenile chronic arthritis". March 2011 – start of baseline therapy with sulfasalazine (30 mg/kg per day, or 0.5 g/day), nonsteroidal anti-inflammatory drugs (NSAIDs: diclofenac (intramuscularly), than Voltaren (per os)); intraarticular Diprospan injections into right knee and right wrist joints. In the course of the treatment - positive dynamics at first; May 2011 - development of a marked exacerbation; hospitalization to a specialized federal rheumatology hospital. Examination revealed moderate laboratory activity (ESR – 22 mm/h, Hb – 96 g/l), oligoarticular joint lesion accompanied by formation of a flexion contracture in the knee joint (the girl could barely walk) and bilateral uveitis (for the first time). Prescriptions: local eye therapy (Maxidex, Indocollyre). Addition of methotrexate (subcutaneous injections; 6 mg/week) to baseline sulfasalazine therapy. December 2011 – another disease exacerbation with active bilateral uveitis. Withdrawal of sulfasalazine, prescription of cyclosporine A (3.3 mg/kg per day, or 60 mg/day), right knee joint puncture with administration of glucocorticoids. May 2012 – hospitalization with clinical pattern of active oligoarthritis and uveitis. Prescription of genetically engineered biological preparations (adalimumab) was under discussion; pulse therapy with methylprednisolone (93-62 mg, No. 3) implementation; continuation of combined baseline therapy with methotrexate (7mg/week) and cyclosporine A (60 mg/day). Despite the conducted therapy, polyarticular joint syndrome with maximum manifestation in the right knee joint and flexion contracture formation persisted. The girl was under regular observation at the Helmholtz research institute of eye diseases and continued undergoing local eye therapy (Maxidex TID, Indocollyre BID); uveitis exacerbation would develop in the event of glucocorticoid instillation rate reduction down to 2 times per day. Since August 2012 the girl has been observed at the RAMS Nasonova Research Institute of Rheumatology (Federal State Budgetary Institution). Intraarticular triamcinolone acetonide injection (20 mg) was performed on the pre-hospital stage. The girl was for the first time hospitalized to the Institute of Rheumatology in October 2012. No considerable therapy correction due to sufficient effect of the performed intraarticular injection. November 2012 another disease exacerbation characterized by development of knee and ankle joint arthrites and

quantitative progression (involvement of cervical spine in the process) after an ARVI. January 2013 – another hospitalization to the Institute. Examination revealed asymmetrical polyarthritis with lesions of knee ankle joint and right knee joint and flexion contracture formation, relative elongation of the right lower extremity (+ 2 cm) and dactylites of the $2^{nd}-3^{rd}$ hand digits along with restraint of cervical spine movement with marked pain syndrome, marked laboratory activity (ESR - 30 mm/h, C-reactive protein - 52.3 mg/l), HLA B 27 - negative, ANF - 1/320. X-ray examination of hands: hypertrophic metaphyses of several maniphalangeal bones. Magnetic resonance imaging (MRI): proximal phalanx bone marrow edema of the 2nd right hand digit, symptoms of synovitis of the 3rd left hand digit (pic. 1-5). Taking into consideration polyarticular nature of the lesion, progression of clinical and functional disorders accompanied by knee joint flexion contracture and local growth disorders and symptoms of periostitis in the third hand digit areas accompanied by active uveitis, methotrexate therapy was complemented with adalimumab (30 mg subcutaneously once per 2 weeks) – human monoclonal antibodies to tumor necrosis factor (TNF) α. Cyclosporine A was withdrawn. The patient has been receiving adalimumab (good tolerability and efficacy) since 21.01.2013. Please note that the first 2 adalimumab injections were followed by considerable decline of arthritis manifestations and termination of uveitis activity, whereas in the subsequent 2 months the effect slightly regressed. Moderate manifestations of right knee and left ankle joint arthrites persisted and ESR remained at 22 mm/h, which is why adalimumab dose was increased to 40 mg per administration (March 2013). Examination in June 2013 revealed termination of the pain syndrome and recovery of joint appearance and function and normal motion range in cervical spine. Within the next 6 months further positive condition dynamics without symptoms of joint syndrome activation was observed. Minimal defiguration in the third hand digit areas without restraint of movement persisted. The difference in extremity length almost completely compensated and laboratory parameters normalized in the setting of linear growth acceleration (pic. 6). Stable uveitis remission was achieved; this allowed withdrawing local eye therapy. November 2013 scheduled examination involving X-ray and MR imaging detected no local inflammatory activity and osteitis manifestations (see pic. 5).

Disease in our patient's mother described below featured similar clinical manifestations in the disease onset, which, however, resulted in severe irreversible consequences. The scheme of clinical history is shown on the picture 7.

Patient A.E., born in 1978, has been having the disease since the age of 3, the disease set on with right knee joint arthritis; polyarthritis with lesions of ankle, knee and hip joints along with several smaller hand and cervical spine joints developed after 2 years into the disease. Bilateral uveitis appeared 3 years after the disease onset; it was quickly complicated by bilateral cataract, which was operatively treated (OS in 1989, OD in 1997). The patient has been being observed at the Institute of Rheumatology since 1989 (11 years of age) with diagnosis "Juvenile rheumatoid arthritis with eye lesion". The patient had been undergoing course NSAID treatment and intraarticular glucocorticoid injections, had been successively receiving various baseline drugs (Delagil, Chlorbutin, methotrexate, azathioprine, Tauredon, sulfasalazine and cyclophosphan (intravenously and intramuscularly)) and pulse methylprednisolone therapy. She has been receiving prednisolone (10-5 mg/day) on a regular basis since 1996 (18 years of age). Despite the complex therapy, joint syndrome and laboratory activity (ESR - 40-50 mm/h) persisted. Marked condition aggravation was observed after the first childbirth (at the age of 22 years), when the examination revealed ankylosis of cervical spine and sacroiliac joints and aseptic left whirlbone necrosis for the first time. Diagnosis was changed to ankylosing spondylitis. Antigen HLA B27 – negative. 2004 – endoprosthetic left hip joint replacement. 2009 – another marked exacerbation after the second childbirth (ESR - 53 mm/h, aseptic right hip joint necrosis). 2009 endoprosthetic right hip joint replacement. Arthritis had been persisting for the next 4 years with maximum manifestation in the right knee joint. April 2013 – prescription of adalimumab (40 mg once per 2 weeks). Significant positive dynamics characterized by pain syndrome termination, lack of morning stiffness, joint syndrome minimization and reduction in inflammatory activity

markers values was observed in the course of the therapy. The main clinical manifestations and radiological examination data with commentaries are given in pic. 8-13.

DISCUSSION

The given clinical observation of a family case (mother and daughter) of juvenile arthritis and uveitis is rather instructive in several aspects. On the one hand, anamneses morborum of both patients strike with a completely the same set of disease onset symptoms, including succession of involvement of different joints and cervical spine, uveitis development and even the same dominant joint lesion (the highest degree of manifestation in the right knee joint as the primary lesion object and high dactylites intensity with symptoms of periostitis of the 3rd left hand digit). On the other hand, these two clinical observations clearly and strongly demonstrate the progress of pharmacotherapy of rheumatic diseases achieved in the last 30 years. The "modern" anamnesis of the girl in question demonstrates resistant course of the disease, which may be overcome only with genetically engineered biological preparations (GEBPs) capable of precise (target) immunomodulation. Despite consecutive use of the modern traditional pharmacotherapy methods, the disease acquired a steadily progressive course, whereas additional radiologic visualization methods allowed confirming extension of inflammatory alterations (pathological process) not only to articular and tendinous-ligamentous structures, but also to bones. Osteitis manifested clinically with dactylites symptoms, radiologically – with proximal maniphalangeal periostitis, is usually characterized by torpidity to therapy and high risk of bone destruction (to the extent of osteolysis). In combination with polyarticular (although limited) lesion and flexion contracture of a large joint with local bone growth disorders, this clinical variant should be seen as prognostically unfavorable, requiring addition of GEBPs to the therapy. Nature and localization of joint syndrome, particularly, its asymmetry and dactylites, which are often associated with risk of psoriatic arthritis manifestation. conditioned choice of GEBPs as TNFinhibitors, whereas uveitis and small age conditioned exclusive use of adalimumab. Despite the background therapy reduction (cyclosporine A withdrawal), prescription of adalimumab therapy resulted in an almost complete termination of both joint and ophthalmic lesions.

Development of modern technologies allowed revealing one of the most important symptoms of osteoarticular system lesion even in preschool-aged children using MR imaging in routine practice. Anesthesia is not indispensable. Detection of bone marrow edema is of special importance due to potential negative prognostic value indicating a possibility of destructive lesion in the future [16, 17]. Therefore, this paraclinical symptom is an additional reason for prescribing a more aggressive therapy ceteris paribus.

Complete normalization of MR signal reflected from the previously altered zone is observed in our patient after 10 months due to considerable therapy correction. X-ray examination did not yield any evidence for appearance of destructive disorders or altered osteoarticular system development. All the aforementioned facts hold out a hope that the timely prescribed therapy has significantly affected the disease course.

The achieved effect is especially indicative in the context of the disease's clinical pattern in the patient's mother, who developed the same clinical variant of JA 30 years before her daughter and was once a patient at the Institute of Rheumatology. More than 30 years of the disease development in this patient is characterized by dramatic complications of joint and eye lesions. Severity of ophthalmic pathology consequences is exceptional; it is not often encountered in clinical practice and literature data [18]. Nosological outcome was rather unexpected for this clinical subtype of JA. No reliable similar data on such nosological outcomes can be found in foreign literature. Among the national authors we may mention the work by E.Yu. Loginova [19] demonstrating that such patients may, as adults, develop clinical pattern with both seronegative rheumatoid arthritis and spondyloarthritis features. In that trial the author points out development of polyarthritis, which is often complicated by severe dysfunctions requiring endoprosthetic replacement of joints (observed in the case of our patient's mother), in patients. The authors

classifies such patients into the group of "genuine chronic juvenile arthrites". The same also concerns psoriatic arthritis in a sense, as it is a separate nosological form found in between rheumatoid arthritis and spondyloarthritis. Proofs of potential ankylosing spondylitis formation in the event of ANF-associated oligo-/polyarthritis at an early age of onset are singular and insufficiently informative. In her work, S.O. Salugina considers the possibility of equifrequent (37.5%) development of both seronegative rheumatoid arthritis and spondyloarthritis at follow-up observation of patients with uveitis [20]. However, its correlation with the possibility of evolution of oligoarticular (in the onset) JA with uveitis into axial spondyloarthritis in a female patient with early age of onset, ANF, negative antigen HLA-B27 and marked peripheral arthritis with erosions is not quite clear. Anamnesis morbi of our patient's mother convincingly indicates the possibility of such a nosological outcome. Despite the lack of factors predisposing development of spondyloarthritis, objective trial data, including complete ankylosis of sacroiliac joints and zygapophysial cervical spine joints and symptoms of symphysitis leave no doubt about diagnosis "ankylosing spondylitis". Late (virtually in the third decade of the disease) manifestation of the disease's nosological nature and, on the contrary, development of the features associated with all JA – development of micrognathism, destructive lesion of hip joints requiring endoprosthetic replacement at a young age and adverse uveitis outcome attracts special attention. Wrist joint lesion and hand dactylites, which are not associated with ankylosing spondylitis, but allow including psoriatic arthritis in the range of differentiated conditions, require mentioning as well. It ought to be noted that neither the patient nor her closest relatives have ever had symptoms, which could have indicated skin psoriasis, throughout more than 30 years of the disease. It should also be mentioned that the hip joint lesions, which were the last arthritis to develop, quickly led to destructive alterations requiring endoprosthetic replacement. This phenomenon may be characteristic of juvenile onset of the disease, regardless of the precise nosological form. The fact that symptoms of hip joint lesions have not been observed in the younger patient may indicate that the adalimumab-involving therapy adequate to nature and prognosis will in the long term help to prevent qualitative and quantitative progression of joint syndrome and avoid severe uveitis complications.

The given clinical observations strongly demonstrate timely active tactics of JA treatment forestalling incapacitating consequences of a severe pediatric disease.

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Pic. 1 – General appearance of hands of patient K.K., 3.5 years of age. The 3^{rd} left hand digit alterations: swelling of proximal phalanx and the 3^{rd} proximal interphalangeal joint with flexion contracture in the latter.

Pic. 2 – X-ray image of hands of patient K.K., 3.5 years of age, anteroposterior projection. Swelling of soft tissues and hypertrophic proximal phalanx of the 3^{rd} left hand digit. Hypertrophic middle phalanxes of 3 hand digits.

Pic. 3-5. MR imaging of hands of patient K.K., 3.5 years of age.

Pic. 3. MRI of the left hand (basic data).

A – sagittal plane (through the 3^{rd} metacarpus).

B – coronary plane. Impulse sequence: GE STIR.

Synovitis of the 3rd metacarpophalangeal joint.

Pic. 4. MRI of the right hand (basic data).

A – sagittal plane (through the 2^{nd} metacarpus).

B – coronary plane. Impulse sequence: GE STIR.

Bone marrow edema of proximal segments, including proximal phalanx diaphysis of the 2nd right hand digit.

Pic. 5. MRI of the right hand. Coronary plane. Impulse sequence: GE STIR. No pathological alterations after 10 months of adalimumab therapy.

Pic. 6 – Appearance of child K.K., 4 years of age. Complete form and function recovery of all joints. Correction of the right knee joint's flexion contracture, compensation of the difference in extremity length.

Pic. 8 – General appearance of hands of patient A.E., 34 years of age. Defiguration of several hand digits and left wrist. Deformation (including altered axis) of the 3rd left hand digit.

Pic. 9 - X-ray image of hands of patient A.E., 34 years of age, anteroposterior projection.

Narrowed cavities of several hand joints (the 1st right metacarpophalangeal joint, intercarpal joints). Erosions of the 1st carpometacarpal and metacarpophalangeal joints. Hypertrophic proximal phalanx of the 3rd left hand digit.

Pic. 10 – Pelvic X-ray image, patient A.E., 34 years of age. Cavities of sacroiliac joints not found (ankylosis). Pelvic ring – locked into a single bone block on the level of sacroiliac joints. Pubic symphysis: subchondral osteosclerosis, irregular articular surfaces, singular cysts (symphysitis). Condition after bilateral total endoprosthetic replacement.

Pic. 11 - X-ray image of knee joints of patient A.E., 34 years of age, anteroposterior projection. Extensive osteoporosis. Narrowing of articular cavities (on the left – insignificant, on the right – marked), subchondral cysts and small osteophytes on the edges of articular surfaces. Irregular articular surfaces on the right.

Pic. 12 – Cervical spine lesion, patient A.E., 34 years of age. Cervical lordosis straightening. Micrognathism.

A – X-ray image of cervical spine, lateral projection. Complete bony ankylosis of the atlantooccipital joint and all zygapophysial joints.

B - MR imaging, T1-weighted mode. MR signal intensity increase in anterior segments of vertebral bodies C2-C3-C4 and in the area of anterior arch of vertebra C1 (symptoms of bone marrow steatosis due to chronic anterior spondylitis). Atlantooccipital joint ankylosis. C – appearance (profile) of the patient's face.

Pic. 13 – Complications of bilateral uveitis in patient A.E., 34 years of age, length of disease – 30 years. Left corneal leukoma. Deformation of the right pupil.

ТЕДИАТРИЧЕСКАЯ ФАРМАК



Примечание. ГК в/с — глюкокортикостероид, внутрисуставное введение; НПВП — нестероидные противовоспалительные препараты.

Рис. 7. Схема истории болезни пациентки А.Е.	Pic. 7. Schematic anamnesis morbi of
(матери ребенка К.К.)	patient A.E. (mother of child K.K.)
Артрит правого коленного сустава	Right knee joint arthritis
Полиартрит, включая тазобедренные суставы и	Polyarthritis including hip joints and
шейный отдел позвоночника	cervical spine
Увеит двусторонний	Bilateral uveitis
Скорость оседания эритроцитов	Erythrocyte sedimentation rate
Лечение	Treatment
ГК в/с	GC (i/a)
Прогрессирующая деструкция, сгибательная	Progressive destruction, flexion
контрактура	contracture
Эндопротезирование тазобедренных суставов	Endoprosthetic replacement of hip joints
Асептический некроз головки бедренной кости	Aseptic whirlbone necrosis
Анкилоз шейного отдела позвоночника и	Ankylosis of cervical spine and sacroiliac
крестцово-подвздошного сочленения	joint
Экстракция катаракты	Cataract extraction
OD – оперированная вторичная постувеальная	OD – postoperative secondary postuveal
компенсированная глаукома, афакия	compensated glaucoma, aphakia
OS – оперированная вторичная постувеальная	OS – postoperative secondary postuveal
глаукома, амавроз, бельмо роговицы	glaucoma, amaurosis, corneal leukoma
НПВП, Делагил, Хлорбутин	NSAIDs, Delagil, Chlorbutin
Метотрексат	Methotrexate
Азатиоприн	Azathioprine
Тауредон	Tauredon
Сульфасалазин	Sulfasalazine
Циклофосфан	Cyclophosphan
НПВП, пульс-терапия ГК	NSAIDS, GC pulse therapy
Преднизолон 5-10 мг/сутки	Prednisolone (5-10 mg/day)
Адалимумаб	Adalimumab
Возраст	Age
Примечание. ГК в/с – глюкокортикостероид,	Note. GC (i/a) – glucocorticosteroid,
внутрисуставное введение; НПВП –	intraarticular administration; NSAIDs -
нестероидные противовоспалительные	nonsteroidal anti-inflammatory drugs
препараты	
Педиатрическая фармакология	Pediatric pharmacology