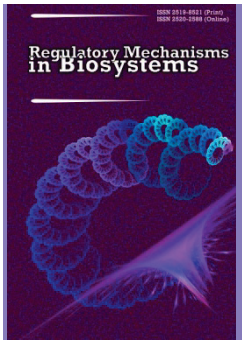

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Systemic juvenile idiopathic arthritis in the pediatric practice of Donetsk region

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Juvenile idiopathic arthritis with systemic onset is a special, rare and the most severe variant of juvenile idiopathic arthritis. The article analyzes the clinical features of the onset and course of juvenile idiopathic arthritis with systemic onset in children living in the ecologically disadvantaged Donetsk region and the efficacy of therapy. Clinical cases are described. According to its clinical manifestations, the systemic variant of juvenile idiopathic arthritis is characterized by the severity of the general inflammatory response, a bright clinical picture, severe damage to internal organs, the development of polyserositis, can lead to the development of life-threatening conditions, such as macrophage activation syndrome, and also leads to the formation of deforming arthritis with early disability of the sick child. The relevance of studying the problem of juvenile idiopathic arthritis with a systemic onset is related to the late diagnosis of the disease, because at the onset of the disease there may be no joint syndrome, and therefore it is impossible to use the criteria of the International League of Rheumatology Associations to verify the diagnosis, which leads to diagnostic errors. Nonsteroidal anti-inflammatory drugs, glucocorticosteroids, and immunosuppressants are used for treatment. The prescription of genetic engineering biological therapy, the choice of the drug, is carried out according to the recommendations of the American College of Rheumatology, depending on the preference for systemic or joint manifestations of the disease. But the question of the optimal approach to regimens of dose reduction, duration of biological therapy, and rules for its withdrawal remains open. Until now, the optimal approach to the treatment of juvenile idiopathic arthritis with a systemic onset is unknown. To date, the issue of treatment in patients with pharmacoresistant variants and persistent course of the disease has not been solved. Therefore, further in-depth study of this problem, optimization of the diagnostic algorithm and an individual approach to therapy are needed.

Keywords: children; systemic juvenile idiopathic arthritis; diagnosis; clinic; course; treatment; tocilizumab; prognosis.

Introduction

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of diseases of unclear etiology, characterized by a complex autoaggressive pathogenesis, with a severe, chronic, steadily progressing course, which begins before the age of 16, leading to destructive and inflammatory changes in the joints that last more than 6 weeks provided that other joint pathology is excluded, with early disability of the sick child and a decrease in the quality of life (Baranov & Alekseeva, 2016; Petty et al., 2016; Bogmat & Shevchenko, 2017).

JIA is a heterogeneous group of connective tissue diseases with the predominant localization of the process in the musculoskeletal system. A special place in the classification of JIA is occupied by the systemic variant of the disease (sJIA). According to the classification of the International League of Rheumatology Associations (ILAR), the diagnosis of sJIA is established in the presence of arthritis accompanied by fever or with previous fever for 2 weeks in combination with two or more signs – unstable erythematous rashes, serositis (pericarditis, pleuritis, peritonitis), generalized lymphadenopathy, hepatomegaly and/or splenomegaly (Petty et al., 2016; Sag et al., 2019; Koniushevska et al., 2022).

Rationale. All over the world, there is a progressive increase in the prevalence of rheumatic diseases in both adults and children. In the structure of rheumatic diseases in children, JIA prevails, the prevalence of JIA in the world is 1–2 cases per 1000 children (Baranov & Alekseeva, 2016; Oshlyanska & Melanchuk, 2019; Oshlianska & Artsymovych, 2020). The annual incidence of JIA is from 1.6 to 23 new cases per 100,000 children, including the incidence of sJIA – 6.6–15 per 100,000 children (Deslandre, 2016).

The regularity of incidence and prevalence of both JIA and sJIA depending on geographical and ecological features is observed. sJIA accounts for 5–15% of all cases of JIA in North America and Europe, the smallest share of sJIA in the structure of JIA is in Sweden – 2.7%, while the largest is in Japan – 50% (Grevich & Shenoi, 2017; Albaker, 2020; Smolewska et al., 2021). The prevalence of sJIA in Europe is 0.3–0.8 per 100,000 children (Alekseeva et al., 2017; Shenoi et al., 2018; Sag et al., 2019). According to Krekhova (2022) the prevalence of sJIA is 1–10 cases per 30,000 children.

So far, no specific etiological factor has been identified that would cause the development of JIA, sJIA. The disease can debut after infectious diseases, injuries, stress, hypothermia. However, these are only external factors that implement internal deep mechanisms. sJIA is a special variant of JIA, which refers to autoinflammatory and not "classic" autoimmune diseases. Therefore, there are significant differences in pathogenesis, features of the course of sJIA, its response to therapy, prognosis and development of complications. The leading role in the sJIA pathogenesis is played by the activation of the innate link of immunity, the development of clinical and laboratory manifestations of the disease is provided by interleukin 1 (IL-1) and interleukin 6 (IL-6) (Gulati et al., 2016; Grevich & Shenoi, 2017; Sullivan, 2018). sJIA is a special rare disease with an unfavourable course. sJIA is the most severe variant of JIA in terms of its clinical ma-

nifestations, which, on the one hand, is characterized by the severity of the general inflammatory response, bright polysyndromy, severe damage to internal organs (myopericarditis, interstitial lung damage), the development of polyserositis (pericarditis, pleuritis, peritonitis), and can lead to the development of life-threatening conditions, such as Macrophage Activation Syndrome (MAS), pulmonary alveolar hypertension and pulmonary alveolar proteinosis; on the other hand, it leads to the formation of deforming arthritis with early disability of the sick child (Alekseeva et al., 2015; Baranov & Alekseeva, 2016; Boiko, 2019).

The urgency of studying the problem of sJIA is also related to the late diagnosis of the disease. According to the criteria of the International League of Rheumatology (ILAR), the diagnosis of sJIA must be verified within 2 weeks from the onset of its first clinical manifestations (Petty et al., 2016; Koniushevska et al., 2022). However, there is no single symptom, no specific laboratory markers of the disease that can unambiguously and quickly confirm the diagnosis of sJIA (Petty et al., 2016; Yusupova, 2019; Koniushevska et al., 2022).

However, at the onset of the disease, there may be no joint syndrome and but there are extra-articular manifestations, which complicates timely diagnosis and leads to diagnostic errors. Therefore, differential diagnosis should be carried out with a number of diseases accompanied primarily by high, prolonged fever (infectious diseases, sepsis, oncohematology, other diffuse connective tissue diseases, etc.) (Alekseeva et al., 2017; Yusupova, 2019; Smolewska et al., 2021). It is very difficult to diagnose sJIA (according to the ILAR criteria) in patients in whom arthritis is absent or is detected quite late. In 50% of patients, due to the absence of arthritis, it is impossible to use the ILAR criteria to verify the diagnosis of sJIA (Hinze et al., 2018; Beketova et al., 2021; Smolewska et al., 2021).

It is worth noting that the diagnosis of sJIA is most often made later than 6 weeks after the onset of the disease. Thus, according to Alekseeva et al. (2015) no patient was diagnosed with sJIA within the first 6 weeks. The diagnosis was verified before 6 months in 76.6% of patients, in the rest of the children – after more than 6 months. According to Lomakina (2017), in the first 2 weeks after the debut of sJIA, only one third of children are suspected. In the second third of patients, the diagnosis of sJIA was established within the first year of the disease.

Infectious diagnoses were initially established in 65% of patients. The majority of patients with sJIA (85%) at the onset of the disease were hospitalized in non-specialist departments, and only 15% – in cardiorheumatic departments (Alekseeva et al., 2015; Lomakina, 2017). That is, there are serious difficulties in the diagnosis of sJIA.

It should also be remembered that complications may develop with sJIA (Okhotnikova & Ponochevnaya, 2018; Schulert et al., 2018; Shimizu et al., 2020). The most dangerous complication of sJIA is MAS – the development of a "cytokine storm" and hemophagocyte, the mortality from which is up to 30% (Baranov & Alekseeva, 2016). Children with a refractory course of sJIA may develop such complications as pulmonary alveolar hypertension, interstitial lung disease, and pulmonary alveolar proteinosis, which are probably associated with impaired alveolar macrophage function due to the inflammatory process on the background of sJIA, with a mortality rate of up to 68% (Grevich & Shenoi, 2017; Boiko, 2019). The overall mortality rate for sJIA is 1% in Europe and 0.5% in North America (Alekseeva et al., 2015; Baranov & Alekseeva, 2016; Petty et al., 2016).

According to various authors, 11% to 40% of patients with sJIA have a monocyclic course and over time the disease ends with recovery; 1/3 of patients (34%) have a polycyclic course, that is, there is an alternation of remission periods and disease activity. But recently, half (up to 55%) of patients develop severe destructive arthritis, continuously relapsing, i.e. persistent course, when remission never occurs and early disability of the child occurs. The frequency of destructive changes in the joints when the disease is 5–10 years old varies within the range of 63–75%. This leads to limitation of the movement and self-care possibility, physical, mental, and social maladaptation of children and reduces their quality of life (Salugina, 2012; Alekseeva et al., 2017; Shenoi et al., 2018).

JIA significantly affects the growth and physical development of the child. According to a study conducted in the USA, 17% of children with a disease duration of more than 5 years were stunted (below the 5th percentile), and the greatest deviations were found in patients with sJIA – 50%, 16% – with polyarthritis, and 11% – with oligoarthritis. This was facilitated by the duration and activity of the disease, as well as the side effect of glucocorticosteroids (GCS) (Salugina, 2012; Albaker, 2020; Marushko & Holubovska, 2020). Osteopenic syndrome was found in 28.6% of children with JIA, and vitamin D deficiency in 88.6% (Shevchenko et al., 2021).

It should be noted that the treatment of sJIA still remains a difficult task. In modern pediatric rheumatology practice, the purpose of treating children with JIA is to achieve rapid and complete clinical and laboratory remission or to achieve low disease activity and disease control (Ringold et al., 2013; Onel et al., 2022).

Nonsteroidal anti-inflammatory drugs (NSAID), corticosteroids, and immunosuppressants are used to treat sJIA (Ringold et al., 2013; Kaleda et al., 2019; Onel et al., 2022). But NSAID and GCS do not control the course of JIA and do not prevent the development of bone-cartilage destruction (Bogmat & Shevchenko, 2017; Koniushevska et al., 2022). Traditional cytostatics methotrexate (MTX), which has acquired the status of the "gold standard" of basic therapy, the "number one" drug for the treatment of JIA, is not effective in sJIA with active systemic manifestations without arthritis (Grevich & Shenoi 2017; Ferrara et al., 2018; Albaker, 2020). Long-term use of oral corticosteroids leads to the development of severe adverse events – growth retardation, obesity, hypertension, the development of osteoporosis, steroid diabetes, etc. (Baranov & Alekseeva, 2016; Nigrovic et al., 2018; Oshljanskaja, 2018). Steroid resistance or steroid dependence often develops (Ringold et al., 2013; Bogmat & Shevchenko, 2017; Grevich & Shenoi, 2017). But despite everything, it is still impossible to completely abandon the use of GCS in case of sJIA (Bogmat & Shevchenko, 2017; Kimura et al., 2017; Albaker, 2020).

The emergence of genetically engineered biological drugs (GEBD) made it possible to avoid long-term use of GCS, prevent the further development of the disease and its complications, and change the prognosis of JIA (Grevich & Shenoi, 2017; Smolewska, et al., 2021). The appointment of biological therapy, the choice of the drug, is carried out according to the recommendations of the American College of Rheumatology (ACR), updated in 2021, regarding the prescription of GEBD, depending on the variant of JIA, and in the case of sJIA – depending on the preference of systemic or joint manifestations of the disease (Ringold et al., 2013; Onel et al., 2022).

Different treatment options, including GEBD, are proposed for the three phenotypes of sJIA (Albaker, 2020; Onel et al., 2022). Patients with sJIA without signs of MAS are recommended to be prescribed IL-1 or IL-6 inhibitors, with a possible "switch" to another biological agent if the prescribed GEBD is insufficiently effective. And oral corticosteroids (in a minimal dose and a short course) are conditionally recommended as an initial option of therapy. In the USA and Canada, based on the CARRA registry, 4 standardized treatment regimens for patients with sJIA were developed: (1) GCS only; (2) methotrexate with or without GCS; (3) IL-1 inhibitors with or without GCS; (4) IL-6 inhibitors with or without GCS (Nigrovic et al., 2018; Albaker, 2020; Maritsi et al., 2020).

There are significant differences in the treatment of sJIA, due to the heterogeneous and unpredictable course of the disease. Not all patients respond to treatment with GEBD. Even with the use of modern treatment regimens, half of the patients have an active form of the disease after one year of GEBD therapy. Therefore, it is necessary to identify prognostic factors of the response to GEBD therapy with different mechanisms of action, to identify predictors of "early" response and efficacy of GEBD (Saccomanno et al., 2019; Albaker, 2020).

The issue of the optimal approach to dose reduction regimes, duration of biological therapy and its withdrawal remains open (Ruperto et al., 2018; Kaleda et al., 2019; Song & Lee, 2021). The issue of feasibility of using GCS is discussed, taking into account the occurrence of GEBD. The problem of resistance to the IL-6 blocker – tocilizumab (TCZ, Actemra) exists in 10% of patients, which requires the prescription of IL-1 blockers (Nigrovic et al., 2018; Ruperto et al., 2018; Song & Lee, 2021). But neither anakinra nor canakinumab is registered in Ukraine (Bogmat & Shevchenko, 2017; Oshljanskaja, 2018). Until now, the optimal approach to the treatment of sJIA is unknown, especially taking into account the different initial characteristics of the patient. The issues of treating patients with pharmacoresistant variants of the disease and with a persistent course of sJIA also remain unresolved today (Albaker, 2020; Smolewska et al., 2021; Pawlocik et al., 2023).

Thus, early recognition of sJIA and early prescription of adequate antirheumatic therapy, including biological therapy, is necessary for successful control of the disease, and also affects the course and prognosis of sJIA.

The purpose of the study is to reveal the clinical features of the debut and course of sJIA in children in the city of Mariupol, in the conditions of the ecologically disadvantaged Donetsk region, Ukraine.

Materials and methods

The study was carried out in accordance with the ethical principles of the Declaration of Helsinki in the 2013 edition (www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects). Informed consent of parents and children was obtained for carrying out the study. The research program was approved by the Ethical Committee of the Medical Faculty of the Donetsk National Medical University.

Under supervision were 88 children with JIA who lived in the ecologically disadvantaged industrial Donetsk region and were treated at the Mariupol Territorial Medical Association "Child and Woman's Health". Of them, 8 children had the rare and most severe variant of the disease – sJIA. The diagnosis of JIA was verified according to the criteria of the International League of Rheumatology Associations (ILAR), 1997. Determination of JIA clinical variants was carried out according to the diagnostic criteria of JIA (Edmonton, 2001). JIA activity was determined by the JADAS (Juvenile Arthritis Disease Activity Score) scale. In addition to traditional laboratory parameters (clinical blood analysis, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), biochemical blood parameters, urinalysis), an immunological study was carried out, which included the study of rheumatoid factor (RF), anti-nuclear antibodies – ANA, interleukin 1 (IL-1) and interleukin 6 (IL-6), tumour necrosis factor-alfa (TNF-α). The presence of HLA B27 was determined. All children were examined by an ophthalmologist. X-ray, ultrasound, electrocardiography (ECG) were used among the instrumental methods. CHAQ (Children Health Assessment Questionnaire) was used to assess the child's functional status. The efficacy of the therapy was evaluated according to the pediatric criteria of the American College of Rheumatology – ACR pedi.

Due to the rarity of this pathology and due to the small sample, the statistical analysis of the results included the calculation of mean values and standard deviations.

Results

From 2010 to February 2022 at the Mariupol Territorial Medical Association "Child and Woman's Health" 88 children with JIA were treated from the age of 11 months to 16 years. 8 children had sJIA. Systemic JIA was detected in 7 girls and in 1 boy. They were children from the industrial cities of the Donbas. No child had a family history of the diseases of the joints and supporting-motor system. The onset of the disease in all children was in the cold period of the year (September–February), obviously this is connected with provoking factors, in almost all patients (7 out of 8) acute respiratory viral infections (ARVI) preceded the disease. The mean age of sJIA onset was 4.2 ± 1.1 years (from 2.0 years to 6.5 years). The duration of observation ranged from 5 to 16 years (9.9 ± 1.3, Table 1).

In only 1 patient, a boy aged 3 years and 10 months, did sJIA proceed as a classic allergoseptic variant of the disease, with a predominance of pronounced active systemic manifestations at the onset of the disease, with arthralgia and in the onset of a delayed joint syndrome, with a polycyclic course and a long remission with the cancellation of the basic and pathogenetic therapy. Classic Still's syndrome with moderate fever, with limited visceritis, but with pronounced polyarthritis with damage to the small joints of the hands, wrist, knee and ankle joints, with a continuously progressive course, and then at the age of 7 years and 7 months with damage to the cervical spine, upper jaw, hip joints, was observed in 1 child, a girl, with the onset of the disease at 3 years and 2 months. But the largest share of the patients (6 out of 8) had sJIA with active systemic manifestations and varying degrees of arthritis activity, with a persistent course and the formation of chronic polyarthritis. A monocyclic course of the disease was not observed in any child with sJIA. Clinical manifestations of sJIA are diverse. At the onset of the disease, all the children with sJIA had a high level (3rd degree) of disease activity, class 2 functional impairment (FI 2). The onset of the disease was manifested by hectic fever, skin syndrome, lymphadenopathy, polyserositis, and hepato- and splenomegaly. All patients had an acute onset with febrile or hectic fever, only 1 girl had a subacute onset, the temperature did not exceed 38.5ºC. The fever lasted an average of 2 weeks, but in 1 child it lasted up to 3 months. Five patients had a rash – spotty, short-lived, mainly at the height of the temperature, localized mainly on the skin of the limbs and trunk; including 1 patient having a linear rash. All patients had lymphadenopathy and hepatolienal syndrome. Acute leukemia was ruled out in 1 child, 4 children were initially admitted to the infectious disease department. On average, the diagnosis of sJIA was made 3.6 ± 1.6 months after the onset of the disease (from 1 to 8 months).

All organs and systems can be involved in the pathological process of sJIA, there can be serositis of varying degrees of severity, which determines the severe course of this variant of the disease. In the studied group of children with sJIA, 1 patient had myocarditis, 1 patient had hepatitis, 1 patient had splenic infarction, 2 patients had alveolitis, 1 patient developed acute pancarditis, exudative pericarditis, with dilatation of heart chambers, rhythm disturbance, and circulatory failure – CF 2a.

The joint syndrome was characterized by a variety of manifestations: from transient arthralgias to severe deformations of the joints (Fig. 1).

Any joint can be a target of sJIA, but most often at the onset of the disease, knee joints (in 8 patients), ankle (in 7 out of 8 patients), and carpal joints (in 6 out of 8 patients) were involved in the inflammatory process. Elbow joints (in 1 patient), shoulder joints (in 1 patient) and small joints of the hands (in 2 patients) were much less often involved in the inflammatory process. Most often, the patients had unilateral, non-symmetrical damage to the joints (except for the hands joints damage).

Limitation of opening the mouth, pain when chewing, which indicates the involvement of the temporomandibular joints, was found in 1 patient with sJIA. 6 out of 8 patients had pain in the cervical spine, impaired neck movement. Pain in the hip joints was detected in 4 out of 8 patients only in case of sJIA recurrences, in the 2nd–4th year of the disease. Damage to the hip joints or the cervical spine in JIA indicates a severe course of the disease, the development of a systemic form of the disease, generalized arthritis.

The mean number of active joints at the onset of the disease was 3.6 ± 1.1. Pain, swelling, impaired mobility of the joint, impaired gait were found in all patients. Morning stiffness, which is defined as a short-term lameness with feelings of numbness, pain in one or more joints, being a classic manifestation of the inflammatory process, was determined in all patients, but it was pronounced throughout the day in 3 patients.

In a number of cases (3 out of 8 patients), delayed joint syndrome was observed, which occurred several months after the onset of systemic manifestations. Exudative changes predominated in the joints, deformations and contractures formed later.

Functional capacity was determined according to the Steinbrocker classification and using the CHAQ – health assessment questionnaire. At the onset of the disease, serious problems with limitation of movements and severe pain (CHAQ index 1–2 points) were noted in all patients, and corresponded to class 2 functional impairment (FI), but after the start of treatment, a decrease in the index of functional insufficiency was observed. The aggressiveness of joint pathology is determined both by the number and nature of joint damage, and by the degree of laboratory inflammatory activity. Children with sJIA are children with a high 3 degree of disease activity at the onset of the disease. All patients (n = 8) had a systemic inflammatory process with an extremely high degree of laboratory activity in the form of significant leukocytosis (from 25.0 to 42.8 x 10^9/L, n = 8) with a neutrophil shift to the left (up to 10–15% of stab neutrophils leukocytes), thrombocytosis (400–560 x 10^9/L, n = 6), progressive anemia (decrease in hemoglobin (Hb) to 70–90 g/L, n = 4), significant increase in ESR (from 25 to 87–127 mm/h, n = 8). An increase in acute-phase indicators (CRP – 3+, 4+; 15.0–78.7 mg/L; seromucoid – 11.6–33.9 units, n = 8) is characteristic, a decrease in iron in blood serum to 3.7 μmol/L (n = 3). One girl developed MAS with typical clinical and laboratory manifestations after chickenpox.

Table 1
Demographic and clinical characteristics of patients with JIA, who were treated at the Mariupol Territorial Medical Association "Child and Woman's Health" from 2010 to February 2022

Indices	Number of patients with JIA n = 88	P, %	Number of patients with JIA, n = 8
Girls	60	68.2	7
Boys	28	31.8	1
Ratio	2:1	2:1	7:1
Urban dwellers	73	83.0	7
Rural dwellers	15	17.0	1
Ratio	5:1	5:1	7:1
Deseases was preceded by			
– ARVI	39	44.3	7
– factor was not detected	32	36.4	1
– preventive vaccination	7	7.9	–
– trauma	10	11.4	–
JIA type			
– polyarticular	40	45.5	–
– oligoarticular	28	31.8	–
– enthesitis-related	9	10.2	–
– systemic variant	8	9.1	8
– psoriatic arthritis	2	2.3	–
– undifferentiated	1	1.1	–
Diagnosis established, months	11.5 ± 4.0	–	3.6 ± 1.6
Mean number of active joints at the onset of disease	6.7 ± 1.1	–	3.6 ± 1.0
The joints damaged most frequently:			
– knee joints	79	89.8	8
– hip joints	26	29.5	4*
– ankle	58	65.9	7
– radiocarpal	34	38.6	6
– temporomandibular	6	6,8	1
– cervical spine	29	33.0	6
– elbow joint	12	13.6	1
– shoulder	6	6.8	1
– small joints of the hands	13	14.8	2
Damage to internal organs and systems**:			
– myocarditis	1	–	1
– hepatitis	1	–	1
– splenic infarction	1	–	1
– alveolitis	2	–	2
– pancarditis	1	–	1
– exudative pericarditis	1	–	1
Fever:			
– hectic	7	8.0	7
– moderate	58	65.9	1
– without fever	23	26.1	–
MAS	1***	1.1	1
Rheumatoid uveitis	12	13.6	1
Development of uveitis 3 years after the onset of joint syndrome	9	10.2	–
Development of uveitis 13 years after the onset of joint syndrome	1	1.1	1
The development of uveitis preceded the joint syndrome for 2 years	2	2.3	–
The mean age of JIA onset, years	5.6 ± 1.2	–	4.2 ± 1.1
Duration of observation, years	5.3 ± 1.0	–	9.9 ± 1.3

Notes: * – damage to the hip joints developed only with sJIA relapses in the 2–4th year of the disease; ** – internal organs and systems were affected only in children with sJIA; *** – MAS developed only in a child with sJIA.

RF was negative in all patients with sJIA (seronegative variant of the disease). ANA – a positive variant of the disease was present in 1 patient, a boy with sJIA with active systemic manifestations (allergoseptic variant), in whom eye damage (uveitis) developed 13 years after the onset of the disease, and the ANA titer increased 1.5 years before the eye damage to 1:160 – 1:320. All patients had an elevated level of IL-6 from 23 to 168 pg/mL (normal to 7 pg/mL), but the level of IL-1 was normal. Along with a significant increase in the level of IL-6 (168 pg/mL), in 1 child, a girl with persistent sJIA, with limited visceritis and progressive polyarthritis, the level of TNF-α was simultaneously increased to 25.5 pg/mL (normal to 8.2 pg/mL).

During the course of the disease, the frequency of systemic manifestations decreased, and the articular lesion came to the fore. Analysis of the X-ray picture of the disease in the long term showed that classic structural changes of the joints were found in all patients with sJIA. Thus, the first radiological stage of the disease with minimal changes, with epiphyseal osteoporosis, compaction of periarticular soft tissues of the affected joints was found in 3 patients. X-ray stage II with narrowing of the joint space, isolated bone spurs of the affected joints was diagnosed in 2 patients. 3 patients had X-ray stage III with widespread osteoporosis, pronounced bone-cartilage destruction, and systemic bone growth disorders.

In all patients, the inflammatory process in the joints was confirmed by ultrasound examination of the joints. Signs of synovitis with a predominance of the exudative component were detected at the onset of sJIA in most patients (7 out of 8), the exudative-proliferative process was diagnosed in the later stages of the disease in 4 patients, degenerative and destructive manifestations were determined in 3 patients and confirmed by X-ray examination. The degree of joint deformity depends on the type and nature of the inflammatory process: exudative or exudative-proliferative synovitis is clinically manifested as an increase in the volume of the joint with periarticular edema. With a predominance of proliferative-sclerotic changes in the joint, the process can proceed as "dry synovitis" and manifest itself mainly by limitation of movements and severe pain.

On average, the diagnosis of sJIA was established 3.6 ± 1.6 months (from 1 to 8 months) after the onset of the disease. Immediately after the diagnosis was verified, basic therapy was prescribed to all patients.

All children with sJIA received and are still receiving MTX at a dose of 15 mg/m^2/week. The mean duration of MTX therapy was 48.8 ± 10.5 months.

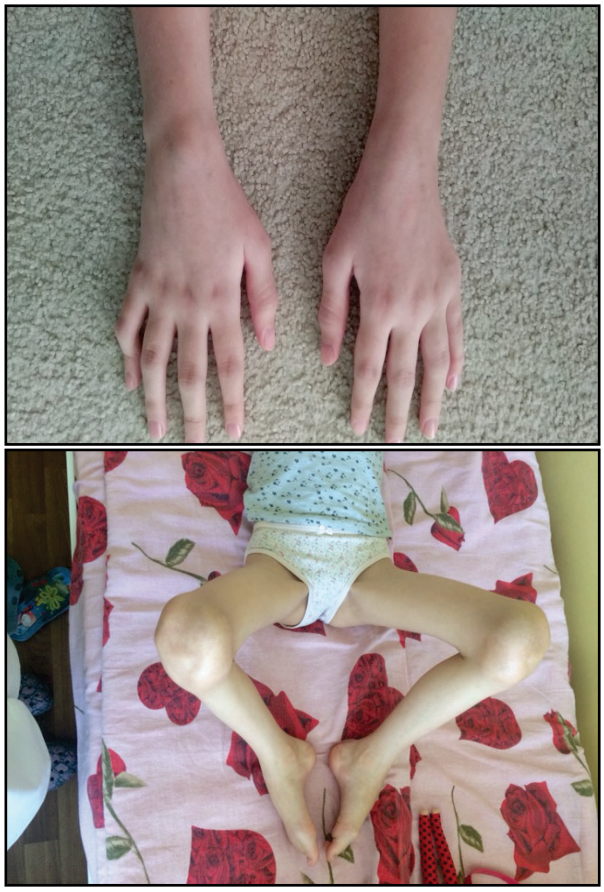

Fig. 1. Joint damage in sJIA in a 9-year-old child (knee, ankle, hip, carpal, hand joints), onset of the disease from the age of 3, progression of the disease in connection with the cancellation of therapy by the parents

All children with sJIA were treated with pulse therapy with GCS – solu-medrol (methylprednisolone) 10 mg/kg intravenously per day for 3–5 days, followed by a transition to 0.5–1.0 mg/kg/day, lasting no more than 1–2 months. The maintenance dose of GCS was 0.10–0.15 mg/kg/day. The mean duration of GCS therapy, taking into account the maintenance dose, was 36.1 ± 11.7 months, because ¾ of the patients had hormone dependence, and when the maintenance dose of GCS was withdrawn, deterioration of clinical and laboratory indices and relapses of the disease were noted.

The presence in children of unfavourable prognostic factors of the disease course, such as high activity of the process and insufficient efficacy of therapy for 6 months, significant active systemic manifestations for more than 6 months, damage to the hip joints or the cervical spine, the presence of erosions and narrowing of the joint space during X-ray examination, is an indication for prescription of GEBD. Tocilizumab was used to treat sJIA. Tocilizumab (Actemra), produced in Switzerland – recombinant humanized monoclonal antibodies to the IL-6 receptor, registered in Ukraine for the treatment of sJIA from two years. Tocilizumab was administered to 8 patients with sJIA intravenously at the dose of 8 mg/kg for a child weighing more than 30 kg or 12 mg/kg for a child weighing less than 30 kg, the infusion was carried out once every two weeks. The mean duration of tocilizumab therapy was 33.2 ± 10.0 months. In one patient with continuously progressive course, hormone dependence, refractory sJIA, the therapy was changed to Janus kinase inhibitors (JAKs) Xeljanz (tofacitinib) and leflunomide, which led to improvement of the child's condition.

Against the background of therapy, significant positive clinical and laboratory dynamics were noted. Systemic manifestations were eliminated in all patients, medical clinical and laboratory remission with complete cancellation of corticosteroids, tocilizumab, but preservation of methotrexate, was achieved in 2 patients. In 1 patient, after the complete cancellation of drug therapy, a relapse of the disease developed after 6 years of stable drug-free remission. In 6 patients, the disease is not acute, but there is a persistent, slowly progressive course of the disease with multiple lesions of the joints, which requires further monitoring and therapy. Each child had worsening of the condition and relapses of the disease, which developed most often against the background of ARVI (n = 8), when the dose of GCS was reduced (n = 6), in case of independent cancellation of therapy by the parents (n = 1). It should be noted that if the child has a source of infection in the form of multiple carious teeth, it is impossible to achieve clinical improvement even with the use of GEBD (n = 2).

Against the background of the therapy, 1 child had frequent toe panaritiums, a severe osteopenic syndrome, 1 girl had empyema of the gallbladder, and there were no other complications of the therapy.

Diagnosis and treatment of sJIA, the rarest, most complex and severe variant of the disease, is a complex task, the solution of which is possible with knowledge of the clinical polymorphism of the onset and course of the disease, careful diagnostic search, and timely prescription of modern therapy, biological drugs. Therefore, we would like to present the clinical observations of patients with sJIA.

Clinical case No. 1. A patient with a systemic variant of JIA, the observation period was 14 years.

Child N., born in 1998, at the age of 3 years and 10 months, was admitted to the Donetsk Regional Children's Clinical Association on 28.08.2002 with complaints of a dramatic increase in body temperature (39 ºC), pain and swelling in the area of the left ankle and of the right knee joints, a spotted-papular rash that appears at the height of the temperature.

Medical history: The patient has been ill since 30.07.2002, when he developed a febrile temperature, a spotted-papular rash on the skin of the chest and limbs. He was treated for ARVI, but his condition did not improve. On August 8, 2002, pain and swelling of the left ankle and right knee joint appeared, and leukocytosis was detected in the blood test. He received NSAID – orthofen, nise (nimesulid). There was no effect from the therapy. The patient continued to have a high fever, the rash persisted, pain in the left ankle and right knee joints bothered him. He was sent to the Regional Children's Clinical Association of Donetsk for hospitalization.

From life anamnesis: Early anamnesis without features. Suffers from atopic dermatitis, food allergy. He often suffers from ARVI, tonsillitis.

Objective status: Upon admission to the regional children's clinical association of Donetsk, the condition was difficult. High fever. Against the background of fever, a spotted-papular rash appeared on the skin of the trunk and limbs. Swelling and soreness of the left ankle and right knee joints, limitation of movements. Vesicular breathing in the lungs. The boundaries of the heart are not expanded, the tones are rhythmic, muffled. The abdomen was soft, painless, the liver is 2.5 cm below the costal margin, the spleen is 1.5 cm below the costal margin.

The child was examined in the clinic. In the blood analysis – leukocytosis (12.8 x 10^9/L), neutrophilia (stab neutrophils – 5%, segmented neutrophils – 62%), eosinophilia (9%), accelerated ESR (53 mm/h). There was an increase in acute phase indices (sialic acids – 350 units (normal to 270 units), diphenylamine test (DFA) – 0.34 units (normal to 0.31 units), seromucoid – 13.6 units (normal to 5.0 units), CRP – 3+). A change in the coagulogram was detected (prothrombin index 74%, coagulation according to Lee-White – 4 min, autocoagulation test (ACT) for 10 min – 108%). RF is negative, Lupus Erythematosus cells (LE-cells) were not detected. Blood test for sterility – sterile. Other biochemical indices of blood (proteinogram, urea, creatinine, bilirubin, transaminases, calcium, phosphorus, fibrinogen, antistreptolysin-O (ASL-O), circulating immune complexes (CIC), cryoglobulins within the age norm. Ultrasound of internal organs, echocardiography, ophthalmologist's examination – no features. ENT doctor's examination: chronic compensated tonsillitis.

Clinical diagnosis: Juvenile rheumatoid arthritis (JRA), articular-visceral form, allergoseptic variant, RF negative, degree III of activity, functional insufficiency (FI) I; Chronic compensated tonsillitis.

Therapy performed: prednisolone 35 mg per day for 4 weeks, plaquinil (hidroxicloroquina) 100 mg per day, fraxiparin for 10 days, dipyridamole, diclofenac, calcemin, asparkam. Against the background of therapy, the

boy's condition improved significantly. Body temperature normalized, skin rashes, pain in ankle and knee joints disappeared, laboratory indices normalized. Pharmacological clinical and laboratory remission was achieved.

Later, the child was examined several times a year at the Mariupol Territorial Medical Association and the Donetsk Regional Children's Clinical Association. A stable pharmacological clinical and laboratory remission was maintained for 2.5 years. In January 2005, prednisolone and plaquinil were discontinued. In May 2005, after ARVI the child showed laboratory activity of the process: accelerated ESR to 21–25 mm/h, an increase in acute phase indices (sialic acids – 237 units, seromucoid – 5.8 units, DFA – 0.26 units, CRP – 2+); the increase of which was associated with ARVI. There were no complaints.

In December 2005, 11 months after the discontinuation of pathogenetic therapy, he suffered an exacerbation of chronic tonsillitis, joint syndrome, gait disturbances, rashes on the skin of the trunk and limbs, general weakness, and increased body temperature appeared. In the blood analysis: leukocytosis (17.7 x 10^9/L), neutrophilia (stab neutrophils – 28%, segmented neutrophils – 48%), accelerated ESR – 38 mm/h. An increase in acute phase indices was noted: sialic acid – 350 units, seromucoid – 13.3 units, DFA – 0.33 units, CRP – 3+. This condition was regarded as a relapse of the disease, with a high degree of activity. He received pathogenetic therapy – pulse therapy with solu-medrol 1000 mg No. 3, then metipred 28 mg per day for 4 weeks; basic therapy – MTX 7.5 mg/week; NSAID (voltaren, nise), symptomatic therapy.

In January 2009 (after 3 years), basic and pathogenetic therapy were canceled. Deterioration of the boy's condition has been noted since 2014 (6 years after the discontinuation of pathogenetic therapy). On 10.23.2014, the child went through angina. On 10.31.2014, pain in the heart appeared, shortness of breath increased, temperature rose to 39 ºC, general weakness was noted. In a serious condition with a pronounced intoxication syndrome and heart failure, he was brought to the pediatric intensive care unit in Mariupol with a diagnosis of JRA, articular-visceral form, allergoseptic variant, acute pancarditis, exudative pericarditis, circulatory failure – CF 2a. 04.11.2014. He was transferred to the intensive care unit of the Donetsk Regional Children's Clinical Association. The child's condition was very serious, due to intoxication syndrome and heart failure. High fever. The skin was pale, there was a polymorphic rash on the skin of the chest, abdominal wall, and limbs. Pronounced dyspnea of a mixed nature (respiratory rate – 58 per minute). Arthralgia in the cervical spine, shoulder, radiocarpal, elbow joints. Peripheral lymph nodes in all groups up to 1.5 cm in diameter. Vesicular breathing in the lungs. Percussion revealed an expansion of the heart borders in diameter, auscultation revealed a significant muting of heart sounds, tachycardia up to 120 beats per minute. The abdomen was soft, moderately painful in the epigastric region, the liver was 2.5 cm below the costal margin, the spleen was 1.5 cm below the costal margin.

During the blood analysis, hyperleukocytosis (from 30.6 to 42.8 x 10^9/L) was revealed, neutrophilia (stab neutrophils – 9%, segmented neutrophils – 80%), thrombocytosis (from 502 to 560 x 10^9/L), accelerated ESR (40–42 mm/h). RF – 12 IU/mL (negative), LE-cells – not detected, ANA – 1:80 (negative), antibodies to double-stranded native DNA – 11.4 units/mL (normal 0–25 units/mL), CIC – 88 units/mL (normal – up to 60 units/mL). Polymerase chain reaction (PCR): *Chlamydophila pneumoniae* DNA – 1.2 units/mL, *Mycoplasma pneumoniae* DNA – 1.9 units/mL (normal – up to 2.7 units/mL), HBV DNA – not detected, HCV RNA – not detected. High acute phase indices – sialic acid – 350 units, seromucoid – 13.3 units, DFA – 0.35 units, CRP – 4+. Other biochemical indices were within the age norm. ECG – heart rate (HR) 115 per minute, sinus tachycardia, voltage drop. X-ray of chest organs: lungs without infiltration shadows, heart shadow expanded across (cardiothoracic index (CTI) – 55%). Echocardiography – moderate dilatation of heart chambers, ejection function (EF) – 63%, contractility of myocardium is not impaired, slight uneven induration of aortic and mitral valves' leaflets. Mitral insufficiency of the 2nd degree, induration of the pericardial leaves, separation of the leaves along the back wall – 0.66 cm, along the free wall of the left ventricle – 0.44 cm. Pressure in the pulmonary artery – 28.0 mm. Holter monitoring: against the background of sinus tachycardia, 5 single ventricular extrasystoles, 2 supraventricular extrasystoles were registered. There was an impairment of repolarization processes in the form of ST segments depression and the formation of a biphasic T(+/-) wave. Ultrasound of the abdominal organs: echo signs of multiorgan changes – diffuse changes in the liver, pancreas, splenomegaly. Fibrogastroduodenoscopy (FGDS) – erythematous hyperacidic gastroduodenopathy associated with Helicobacter pylori. Ophthalmologist: media and eye fundus were normal.

Clinical diagnosis: Juvenile rheumatoid arthritis, articular-visceral form, allergoseptic variant, with damage to the reticulo-endothelial system (RES), liver, skin, heart (myopericarditis), circulatory failure – CF 2a, arthralgia, RF negative, degree III of activity, FI 2a; Chronic gastroduodenitis, exacerbation; Chronic compensated tonsillitis.

Therapy performed: cytostatics – MTX 25 mg/week; glycosides – digoxin; anticoagulants – fraxiparin; antibacterial therapy – meronem, augmentin, amoxil K, klacid; cardiotrophic drugs – riboxin; diuretics – verospiron; hypotensive – enap (enalapril); other symptomatic means.

Glucocorticosteroid therapy was performed, including pulse therapy, MTX, immunoinflammatory process was partially reduced, which was manifested by a tendency toward normalization of temperature, regression of skin rashes, and a decrease in laboratory activity. In view of recurrent fever, arthralgia in the cervical spine and myopericarditis, which persisted, the therapy was supplemented with an immunobiological drug – Tocilizumab (Actemra). This led to a decrease in signs of heart failure, a decrease in laboratory activity. Re-examination in the clinic in December 2014 – the onset of remission was established, the dose of medrol started to be reduced.

In January 2015, back pain occurred. The patient was admitted to the Mariupol Territorial Medical Association. Objectively: The condition was severe, caused by a painful, osteopenic syndrome. He could not move on his own, did not walk, did not sit. Signs of exogenous hypercorticism were expressed. The skin was pale, dry, numerous striae on the abdomen, limbs, areas of depigmentation, lamellar peeling. Deformation of knee joints (spherical shape, smoothing of contours). The range of motion was full, there were no signs of local inflammation. Atrophy of the lower leg muscles. On the feet, recurrent panaritium of toes I, II, III, ingrown nails. In the lungs, vesicular breathing, the boundaries of the heart were not expanded, the tones were rhythmic, muffled, the abdomen was soft, painless, the liver, spleen were not enlarged.

Examination: blood analysis, urinalysis, biochemical blood tests without any features, RF – 12 IU/mL, HLA B27 – not detected, ANA – positive (1:160 – 1:320 (+), calcium – 1.94–2.37 mmol/L, phosphorus – 2.06–1.37 mmol/L. X-ray of the lumbar spine: Widespread osteochondrosis, retrolisthesis of L5 by 0.3 cm, Spina bifida posterior S1. Widespread osteoporosis. Magnetic resonance imaging (MRI) of the lumbosacral spine: signs of deforming spondylosis, osteochondrosis of the lumbar spine with protrusion of the intervertebral discs L3–S1, Schmorl's hernia of the locking plates of Th11–L4 vertebrae. Osteogenon, calcium-D3-Nicomed, a reduced dose of medrol by 4 mg (to 16 mg per day), planned introduction of Actemra, wearing a corset, restriction of physical activity, semi-bed rest were prescribed.

The child was regularly hospitalized on the premises of the Mariupol Territorial Medical Association for assessment of his general condition, activity of the process and administration of GEBD (Actemra). The last hospitalization was on 05.09.2016. Pain in the lumbar region of the spine was intrusive. Objectively: The condition was severe due to the underlying disease, but positive dynamics were noted. Correct build, tall (174 cm), satisfactorily fed (65 kg). No fever. Pronounced signs of exogenous hypercorticism. Independent movement was difficult due to the pain syndrome. Walked in a corset for 20–30 minutes 2–3 times a day. The skin was pale, numerous striae on the skin of the abdomen, lower limbs, in areas of depigmentation. The skin was dry, lamellar peeling. Atrophy of the muscles of the lower legs. On the feet, recurrent panaritium of toes I, II, III, ingrown nails. Deformation of knee joints (spherical shape, smoothing of contours). The range of motion in the joints was full. There are no signs of local inflammation. Vesicular breathing in the lungs. The boundaries of the heart were not expanded, the tones were rhythmic, muffled. The abdomen iwas soft, the liver and spleen were not enlarged.

Examination: there was no laboratory activity of the process (ESR – 3 mm/h, CRP – negative). Rheumatoid panel: – Fc-fragment of IgG autoantibody IgA (RF) – 0.12 (normal < 1.0); Fc-IgG fragment of IgG au-

toantibody (RF) – 0.06 (normal < 1.0); Fc-fragment of IgG autoantibody IgM (RF) – 0.12 (normal < 1.0); cyclic citrulline peptide (A-CCP), IgG antibodies – <7 U/mL (normal <17.0). IL-6 increased – 26.08 pg/mL (normal up to 7.0 pg/mL). Ultrasound of internal organs without features. Echocardiography: Heart cavities were not dilated, mitral valve leaflets induration, pericardial leaflets induration, EF – 70%. ECG: Sinus rhythm. Diffuse changes in the myocardium. Ophthalmologist's examination: Bilateral partial opacification of the lenses – partial cataract of both eyes. Eye changes were detected for the first time, considered as a result of rheumatoid uveitis, 13 years after the onset of the disease. Currently receiving: medrol 6 mg per day daily (since May 2015); MTX 25 mg per week; actemra 400 mg once a month, eye drops – quinax, taufon, oftan-catachrome (alternating for 1 month), symptomatic therapy.

Clinical diagnosis: Juvenile idiopathic arthritis, systemic variant (allergoseptic variant), with damage to the RES, liver, skin, heart (myopericarditis), CF 2a, arthralgia, with damage to the eyes (partial cataract in both eyes), RF negative, III degree of activity, FI 2a; Chronic gastroduodenitis, incomplete clinical and laboratory remission; Chronic compensated tonsillitis; Osteopenic syndrome. L5 retrolisthesis, deforming spondylosis, osteochondrosis of the lumbar spine with protrusion of the intervertebral discs L3–S1, Schmorl's hernia of the locking plates of Th11–L4 vertebrae; Recurrent panaritium of toes I, II, III.

The peculiarity of the case is the presence in the child with the systemic JIA variant of early onset of the disease (from 3 years old), the course of the disease with pronounced systemic manifestations, with a high degree of the process activity, but without active joint syndrome, the development of relapses of the disease (the 1st relapse 11 months after cancellation of therapy, 2nd relapse 6 years after stable drug-free remission with the development of acute pancarditis, exudative pericarditis, with dilatation of heart chambers, rhythm disturbance, supra– and ventricular extrasystoles, CF 2a), eye damage 13 years after the onset of the disease, development of a pronounced osteopenic syndrome with severe damage to the spine.

Clinical case No. 2. A patient with a systemic variant of JIA, the duration of observation is 14 years.

Child K, born in 1999, was admitted to the Donetsk Regional Children's Clinical Association in January 2005 with complaints of pain and swelling of the radiocarpal, ankle, and knee joints, restriction of movement in them, morning stiffness during the day, an increase in body temperature up to 38 ºC, general weakness, lethargy, pallor.

From the anamnesis of the disease, it is known that in December 2004 she fell ill with ARVI and acute bronchitis. Two weeks after ARVI, hyperthermia up to 38 ºC, an enlargement of lymph nodes and arthritis in the small joints of the hands, radiocarpal, knee and ankle joints with pronounced arthralgias occurred. Significant anemia and high laboratory activity were detected.

History of life without features. Vaccinated according to the calendar. She often suffers from ARVI. Family history is not burdensome.

The girl was sent to the Donetsk Regional Children's Clinical Association. Objectively at the time of admission: the girl's condition was serious. High fever (temperature 38.5–39.0 ºC). Pale. The skin is clean. An enlargement of lymph nodes in all groups with a diameter of up to 2 cm was noted. There were signs of active synovitis. Swelling of carpal, knee, ankle joints and small joints of the hands. Soreness and a sharp limitation of their range of motion, a local increase of temperature over the joints. Gait was impaired. Morning stiffness throughout the day. From the side of the lungs and heart without special features. The edge of the liver was 3.5 cm below the costal margin, the spleen was 2 cm below the costal margin.

The child was examined in the Regional Children's Clinical Association of Donetsk: 1) clinical blood analysis: Hb – 90 g/L, erythrocytes – 3.0 x 10^{12}/L), colour index (CI) – 0.9, reticulocytes – 0.0005 x 10^{9}/L, platelets – 222 x 10^{9}/L, leukocytes – 13.8 x 10^{9}/L, eosinophils – 1%, stab neutrophils – 2%, segmented neutrophils – 69%, lymphocytes – 15%, monocytes – 13%, ESR – 65 mm/h; 2) biochemical analysis of blood: bilirubin, glucose, urea, creatinine, uric acid, fibrinogen, prothrombin index, coagulation, duration of bleeding, calcium, phosphorus, ASL-O within the age norm; 3) RF – negative. No LE-cells were detected. Sialic acids – 450 units, siromucoid – 33.9 units, DFA – 0.48 units, CRP – 4+, CYC – 44 units; 4) IgA – 3.3 g/L, IgG – 16.2 g/L, IgM – 1.1 g/L; 5) PCR: *Chlamydophila pneumoniae* DNA, *Mycoplasma pneumoniae* DNA – negative; 6) blood for sterility – sterile; 7) ophthalmologist: No pathology was detected; 8) ultrasound: The size of the liver was increased due to the right lobe. The structure was homogeneous, increased echogenicity. Moderate thickening of the intrahepatic bile ducts' walls, walls of liver vessels. The edge of the liver was 3.5 cm below the costal margin. The spleen was enlarged, the echogenic structure was normal, the edge was 2 cm below the costal margin. Ultrasound of the abdominal organs revealed echo signs of multiorgan changes – diffuse changes in the liver, pancreas, kidneys and splenomegaly; 9) ECG: HR – 130 per minute, sinus tachycardia. Echocardiography – without features; 10) ultrasound of the joints: active synovitis of both radiocarpal, both knees, both hip joints and small joints of the hands; 11) X-ray of both hands in a direct projection with capture of the carpal joints: osteoporosis of the bone structure of the phalanges' epiphyses, carpal bones, epiphyses of the forearm bones was determined. Thickening and compaction of soft tissues was more likely due to edema and inflammatory compaction of the capsule and periarticular tissues. X-ray signs of JRA – stage I.

Clinical diagnosis: Juvenile rheumatoid arthritis, systemic variant, polyarthritis, degree III of activity, seronegative, without eye damage, Ro-stage I, FI 2. Syndrome of exogenous hypercorticism.

Therapy performed: prednisone (1.5 mg/kg) 35 mg/day for 4 weeks with a subsequent reduction by 5 mg per week to 16 mg of methylprednisolone; MTX 10–15 mg/m^2 (7.5 mg/week), NSAID continued in courses, symptomatic therapy.

In May 2005, she suffered chicken pox with high laboratory activity and relapse of joint syndrome. In this connection, pulse therapy of GCS was carried out – solu-medrol 250 mg per day No. 4, plasmapheresis. During 2005, high activity of the laboratory process (degree II–III) with restoration of polyarticular damage, involving the hip joints, was maintained. In November 2005, pulse therapy of GCS with solu-medrol 250 mg/day No. 5, plasmapheresis was repeated.

Since May 2006, the child has been examined and treated annually at the Institute of Pediatrics, Obstetrics and Gynecology of the National Academy of Medical Sciences of Ukraine in Kyiv. At the time of the first hospitalization, there were contractures of the carpal joints and small joints of the hands, pronounced manifestations of exogenous hypercorticism. She received 11 mg of methylprednisolone for a long time. When trying to reduce the dose of corticosteroids, the joint syndrome returned, high laboratory activity: leukocytosis up to 10–17 x 10^{9}/L, anemia (Hb 90–93 g/L), ESR – 32–65 mm/h, increase in acute phase parameters (sialic acids – 390 units, seromucoid – 11.5 units; DFA – 0.32 units, CRP – 3+); reduction of iron in blood serum to 3.7 μmol/L. ANA, RF, antiphospholipid antibodies and antibodies to double-stranded DNA are negative. The dose of MTX was increased to 10 mg per week. We managed to achieve remission within 1 year. However, after suffering acute stenotic laryngotracheitis in July 2007, hyperthermia and exacerbation of joint syndrome occurred. Increasing the dose of GCS led to partial positive dynamics.

In September 2007, she was hospitalized at the Institute of Pediatrics, Obstetrics and Gynecology of the National Academy of Medical Sciences of Ukraine, where the examination revealed: 1) clinical blood analysis: erythrocytes – 3.25 x 10^{12}/L, Hb – 94 g/L, platelets – 280 x 10^{9}/L, leukocytes – 11.5 x 10^{9}/L, eosinophils – 2%, stab neutrophils – 2%, segmented neutrophils – 68%, lymphocytes – 24%, monocytes – 4%, ESR – 30 mm/h; 2) CRP – 3+, RF – negative, ANA – negative; 3) somatotropic hormone – 0.601 ng/mL (normal up to 8 ng/mL), 17-KS (17-ketosteroids) in daily urine – 8.7 mg/day (normal 1.2–6.0 mg/day); 4) proteinogram, bilirubin, transaminases, sediment samples, urea, creatinine, calcium, phosphorus, blood sugar, CIC, urinalysis – within the age norm; 5) ultrasound: liver – echogenicity of the parenchyma is unevenly increased, small-focal nature of the changes, the edge of the liver was by 2 cm below the costal margin, spleen - the dimensions had not changed, the echogenic structure was normal.

She was discharged from the ward with recommendations to continue taking MTX 10 mg/week, increasing the dose of GCS to 0.7 mg/kg (methipred 12 mg/day) followed by a gradual decrease to 5 mg/day. Re-exacerbation occurred after 6 months (May, 2008) with symptoms of

coxitis in the right hip joint and high laboratory activity (ESR – 35 mm/h, Leukocytes – 10.2 x 10^9/L, CRP – 3+). After 1 year (October, 2009), a diagnosis of somatogenic dwarfism was established.

Growth hormone – 0.26 mIU/L (normal for children >20 mIU/L), growth hormone, night peak – 2.39 mIU/L, growth hormone, load – 0.81 mIU/L, somatomedin C – 112.90 ng/mL (normal 249–642 ng/mL 10–11 years). The mother refused therapy with somatotropic hormone.

During six months, in May 2010, we managed to reduce the dose of GCS to 6 mg per day. In the summer of 2010, a recurrence of joint syndrome was noted.

In connection with this, in November 2010, the basic MTX therapy was replaced with azathioprine at a dose of 50 mg per day (started receiving it in April 2011). In 2011, the stabilization of the process was noted for the first time during the year. A repeated attempt was made to minimize the maintenance dose of GCS when metipred was reduced to 5 mg per day. But in February 2012, after ARVI, the joint syndrome worsened again. Diprospan was administered intramuscularly. GCS could not be reduced to the minimum maintenance dose, the metipred dose was maintained at 6 mg per day. The levels of TNF-α and IL-1 were studied – normal, IL-6 increased – 10.0 pg/mL (reference values 1.5–7.0 pg/mL). During the year without deterioration. The next aggravation was the occurrence of pain in the foot when walking in November 2013, which forced an increase in the dose of GCS – metipred to 8 mg per day. In view of the lack of opportunities, the GEBT was not carried out. In the future, in 2013, 2014, it was not observed.

Since December 2015, against the background of a new aggravation of the disease (pain in the phalanx joints, increasing morning stiffness), the Mariupol Territorial Medical Association initiated the administration of GEBD (tocilizumab 240 mg/month). During the following time, the GCS was gradually discontinued. Examined by endocrinologist, ophthalmologist. Endocrinologist: has been sick since 5 years, growth retardation since 7 years. STH therapy was refused. Physical development is 4 points lower than average age norms. Sexual development: Ax2 Ma3 P3 Me3 (mammary gland conical in shape, has a single straight hair in the center of the axilla, has curling hair on the pubis and labia majora, menses are irregular). Stage III of sexual development according to Tanner. Diagnosis: Somatogenic dwarfism. Ophthalmologist: Media and fundus are normal. Examination with a slit lamp – no pathology was detected.

In May 2017, she was hospitalized at the Institute of Pediatrics, Obstetrics and Gynecology of the National Academy of Medical Sciences of Ukraine. No active synovitis was detected during the examination. The range of motion is reduced in the hip joints (abduction) and radiocarpal joints (extension). Deformation of hands and feet. Gait was impaired. Pronounced hypercorticism, somatogenic dwarfism. Weight 46 kg, height 134 cm (16 years 10 months). From the side of internal organs, without features.

Examined: 1) clinical blood analysis: erythrocytes – 4.05 x 10^{12}/L, Hb – 132 g/L, platelets – 211 x 10^9/L, leukocytes – 6.6 x 10^9/L, ESR – 5 mm/h; 2) biochemical blood analysis: bilirubin, transaminases, cholesterol, urea, creatinine, sugar, calcium, phosphorus, CRP, CIC within the age normal. RF, ANA are negative; 3) IL-6 increased to 36.7 pg/mL (normal – up to 7.0 pg/mL); 4) ultrasound of the joints: active synovitis of the left radiocarpal, left hip, both knee, and both ankle joints; 5) X-ray bone densitometry of the entire skeleton, lumbar spine and hips: densitometric indices of mineral density in the range of widespread osteoporosis; 6) X-ray of both hands in a direct projection with capture of the carpal joints: osteoporosis of the bone structure of the epiphyses of the phalanges, carpal bones, epiphyses of the forearm bones, narrowing of the interarticular spaces due to erosive damage to the cartilage, marginal patterns of the articular surfaces are determined. In the area of the left carpal joint – subluxation of the left ulna. Fibrous ankylosis of the carpal joints. The growth zones of the main phalanges area are mostly open on the right (delayed bone growth). X-ray signs of JIA of both hands – stage III.

Therapy performed: azathioprine 50 mg/day; medrol 1 mg every other day, actemra 320 mg once every 4 weeks, symptomatic therapy.

Clinical diagnosis: Juvenile idiopathic arthritis, systemic variant, activity 0, Ro-stage III, FI 2. Somatogenic dwarfism.

The peculiarity of the case in a child with a systemic variant of juvenile arthritis is the presence of hormone dependence, more than one-time courses of pulse therapy with GCS (solu-medrol), forced long-term use of a maintenance dose of methylprednisolone, and despite this, long-term preservation of high laboratory activity, the inability to achieve remission, progressive course of the disease followed by multiple joint lesions and the development of contractures, hip joint lesions, presence of X-ray signs of stage III joint lesions, significant growth retardation.

Insufficient response to basic therapy, replacement of MTX with azathioprine, achievement of relative clinical and laboratory stabilization of the process only against the background of GEBD therapy (tocilizumab), but with the preservation of active synovitis according to the ultrasound of the joints, these being unfavourable prognostic factors for the course of the disease.

Considering the age of the patients we observed, they were transferred for continuation of tocilizumab therapy under the 18+ program at the National Scientific Center "M.D. Strazhesko Institute of Cardiology".

Clinical case No. 3. A patient with a systemic variant of JIA, the duration of observation was 8 years.

Child V., born on November 1, 2011 (3 years and 2 months), was treated at the Regional Children's Clinical Association in Donetsk during the month from 11.01.2014 until 10.02.2014.

A clinical diagnosis was made: Juvenile idiopathic arthritis, systemic variant, polyartitis with limited visceritis, 3rd stage activity, seronegative, FI 2a. Severe anemia.

Complaints during hospitalization to the clinic: temperature rise to 38 ºC, pallor, general weakness, lethargy, swelling and pain in the knee joints, swelling of the feet and hands, lameness in the morning.

Medical history: the girl fell ill with ARVI in December 2013. From the beginning of January 2014, pain and swelling of the ankle joints occurred, and then the right radiocarpal and knee joints. She was hospitalized at her place of residence in the city of Makievka, and received hepacef, cetrin, and NSAID in the children's department. She was transferred to the Regional Children's Clinical Association in Donetsk, because the joint syndrome persisted.

Life history: a girl from first pregnancy and first delivery, body weight at birth – 3700 g. She developed according to age. She has all preventive vaccinations according to the vaccination calendar. Frequent ARVI. Food allergies (sweets, peaches). Family history is without features.

Objective status: the condition was severe. Pain, swelling, restriction of movement in the hip, knee, carpal, interphalangeal joints of the hands. Pale skin, periorbital shadows. The mucous membrane of the mouth was clean, pink, moist, the teeth were carious. Vesicular breathing in the lungs. Heart sounds are rhythmic, muffled, systolic murmur at the top of the heart. The abdomen was soft, the liver was 5.5 cm below the costal margin, the spleen was 2.5 cm below the costal margin.

Examined in the Regional Children's Clinical Association of Donetsk: 1) blood analysis 20.01.2014: erythrocytes – 4.35 x 10^{12}/L, Hb – 69 g/L, reticulocytes – 0.005 x 10^9/L, platelets – 578 x 10^9/L, leukocytes – 11.5 x 10^9/L, eosinophils – 1%, stab neutrophils – 4%, segmented neutrophils – 57%, lymphocytes – 31%, monocytes – 7%, ESR – 55 mm/g. Blood analysis 02.06.2014: erythrocytes – 5.39 x 10^{12}/L, Hb – 97 g/L, reticulocytes – 0.0005 x 10^9/L, platelets – 540 x 10^9/L, leukocytes – 11.5 x 10^9/L, eosinophils – 2%, stab neutrophils – 1%, segmented neutrophils – 48%, lymphocytes – 39%, monocytes – 10%, ESR – 25 mm/h; 2) general analysis of urine 13.01.2014 – without deviations from the norm; 3) biochemical blood analysis 20.01.2014: total protein – 75.58 g/L, CRP > 6 mg/L, urea – 2.1 μmol/L, creatinine – 42.6 μmol/L, cholesterol – 3.9 μmol/L, total bilirubin – 6.11 μmol/L, AST – 36 U/L, ALT – 15 U/L, blood sugar – 6.5 mmol/L; 4) ASL-O – 200 units/mL; 5) CIC – 98 units/mL; 6) prothrombin time – 20 s, activated partial thromboplastin time – 50 s, fibrinogen – 7.8 g/L, international normalized ratio – 1.56; 7) RF – 12 IU/mL (normal – up to 13 IU/mL), ANA <1:80, TNF-α – 25.5 pg/mL (normal – up to 8.2 pg/mL), IL-6 – 168 pg/mL (normal up to 7.0 pg/mL); 8) PCR: *Chlamydophila pneumoniae* DNA, *Mycoplasma pneumoniae* DNA, HBV DNA, HCV RNA – not detected; 9) ECG 13.01.2014: horizontal electrical position of the heart, sinus tachycardia, heart rate – 160 per minute, changes in the myocardium; 10) ultrasound of the abdominal organs of 01.16.2014: a significant increase in the size of the liver and spleen; 11) regional cardiorheumatologist of 01.22.2014: taking into account the early age of the child, high laboratory activity,

synovitis, lymphadenopathy, hepatosplenomegaly, anemia, all this permits us to diagnose the child with a sJIA, systemic variant, polyartitis with limited visceritis. GCS therapy is indicated – pulse therapy No. 3 with subsequent transition to oral administration of 1.5 mg/kg/day. From 02.05.2014: a 2.5-week course of GCS reduced the manifestations of clinical and laboratory activity. MTX basic therapy is indicated, GCS therapy should be continued at a dose of 1.5 mg/kg/day for up to 4 weeks with a subsequent dose reduction to 4 mg/day.

The therapy performed: GCS – Solu-Medrol 125 mg No. 3 22.01–25.01.2014, metipred 16 mg/day from 26.01.2014 for 4 weeks with a gradual dose reduction, cancellation of GCS – 03.08.2014, methodject 7.5 mg with 02.07.2014, NSAID (voltaren), ferrum-lek, actiferin, totem, folic acid, curantyl, calcium-D_3-nicomed, hepacef, enterogermina. Recommended: metipred 16 mg (8, 6, 2 mg) until 20.02.2014, from 21.02.2014 – 12 mg (8, 4 mg); methodject 7.5 mg s/c 1 time/week; folic acid 5 mg/1 time/week against the background of metoject; panangin ½ tablet two times a day while taking metipred; voltaren 6 weeks; curantyl 2 months; ferrum-lek 5 mL/1 time/day until the normalization of hemoglobin; essentiale 1 month; in the eyes – sensivit 1 drop 3 times/day for two weeks, then solcoseryl gel 2–3 times/day for 2 weeks.

Three months after the withdrawal of GCS, from 14.11.2014, the child's condition worsened – synovitis of the knee, tibia, and carpal joints. Correction of therapy: return to metipred 2 mg/day from 06.12.2014, from 12.12.2014 – s/c MTX with an increase in the dose to 10 mg/1 time/week, NSAID. For the first time since 17.12.2014, the IL-6 inhibitor tocilizumab (Actemra) 80 mg/4 weeks has been prescribed GEBD. The last administration of tocilizumab was on 24.11.2015. In connection with the change of residence, she did not receive tocilizumab, the disease progressed. In 2016, the family returned to Ukraine.

She was hospitalized in the Mariupol Territorial Medical Association on 17.03.2016, the laboratory activity was not high, so it was recommended to continue the prescribed therapy, namely – MTX 12.5 mg/week, metipred 4 mg per day, folic acid. But with the deterioration of the child's condition, she was admitted to the Mariupol Territorial Medical Association on 12.06.2018. There were complaints of morning stiffness during the day, pain in the joints – knee, hip, radio-carpal, interphalangeal joints of the hands. For the first time, there were complaints about restriction of movement in the neck, not being able to open the mouth.

Objectively: the child's condition was serious. Body weight deficit of the II degree, body weight 17 kg, height 120 cm (child 7.5 years old). Morning stiffness during the day, gait disturbance. Deformation of the knee joints in the form of a "ball", deformation of the ulnar, carpal, interphalangeal joints, movement disorders, painful on palpation. Significant limitation of movements in the cervical spine, in the maxillary joints. CHAQ score – 2.25; subjective evaluation by the patient – 50. Skin and mucous membranes were clean, pale. A clear percussion sound over the lungs. During auscultation, breathing was vesicular. Limits of the heart according to age, heart sounds were rhythmic, muffled, systolic murmur at the top of the heart. The abdomen was soft, the liver was 2.0 cm below the costal margin, the spleen was not enlarged.

Examined in the Mariupol Territorial Medical Association: 1) blood analysis of 13.06.2018: erythrocytes – 3.3 x 10^{12}/L, Hb – 97 g/L, CI – 0.88, leukocytes – 8.0 x 10^9/L, eosinophils – 4%, stab neutrophils – 3 %, segmented neutrophils – 57%, lymphocytes – 21%, monocytes – 15%, platelets – 270 x 10^9/L, ESR – 53 mm/h; 2) CRP – 78.66 mg/L, RF – 13.8 IU/mL, ANA < 1:100, A-CCP < 7 units/mL (normal < 17.0 units/mL), IL-6 – 62.4 pg/mL (normal up to 7.0 pg/mL); 3) biochemical indices: total protein – 82 g/L, total bilirubin – 9.5 μmol/L, thymol test – 5.1 units, ASL-O – 595 IU/mL, blood sugar – 4.5 mmol/L; 4) chest X-ray of 18.06.2018: there were no pathological changes in the lung fields. The sinuses were free. The heart was normal. 5) ECG of 14.06.2018: sinus tachycardia. Echocardiography: The location of the chambers of the heart and main vessels was correct. EF – 60%. Global myocardial contractility was preserved. Fibrosis of aortic valve leaflets, induration of aortic and mitral valve leaflets. Tachycardia; 6) ultrasound of the abdominal organs of 13.06.2018: enlargement of the liver, diffuse changes in its parenchyma, slight induration of the bile ducts; 7) ultrasound of the thyroid gland of 13.06.2018: no structural changes were detected; 8) X-ray of the hip joints taken 06.14.2018: the heads of both femurs were deformed, flattened, the necks were shortened, arthrosis changes in the roofs of the acetabulums with their shortening. Varus deformity of the hips; 9) X-ray of both knee joints taken 28.06.2018: the joint spaces were narrowed, the cartilage loosens, the joint surfaces were smooth, the intercanal tubercles are slightly deformed on the left; 10) ultrasound of the hip joints taken 13.06.2018: on the right and left side, there was an exudation in the joints between the front and back layers of the joint capsule, with heterogeneous content, the distance between the outer edge of the hip capsule and the surface of the femoral neck exceeded 5 mm, the synovial membranes were thickened. Exudative-proliferative synovitis of both hip joints; 11) ultrasound of the knee joints taken 13.06.2018: ultrasound signs of loosening, thickening of the synovial membranes on the left and right up to 3.0 mm. Expansion of synovial bags in the area of the upper gyrus on both sides, with heterogeneous contents. Exudative-proliferative synovitis of both knee joints; 12) ultrasound of the ankle joints taken June 13.06.2018: on the left and right sides of the back of the feet, thickening of the synovial membrane, synovial fluid in a physiological volume. Proliferative synovitis of both ankle joints; 13) ultrasound of the interphalangeal joints of the hands taken 13.06.2018: phenomena of exudative synovitis and ligamentitis; 14) endocrinologist 15. 06.2018: delay in physical development. Hypoplasia of the thyroid gland; 15) ophthalmologist 18.06.2018: the fundus is free of pathology, the media are transparent.

Therapy with the inhibitor of IL-6 – tocilizumab (Actemra) was resumed at a dose of 12 mg/kg 1 time/4 weeks intravenously in connection with high laboratory activity, a significant increase in the level of IL-6, and a severe course of the disease.

Clinical diagnosis: Systemic juvenile idiopathic arthritis with a persistent course, with limited visceritis, with lesions of the reticulo-endothelial system, heart, polyarthritis, RF (-), ANA (-), III stage activity, Ro-III stage, FI 3. Hypochromic anemia degree I. Delay in physical development. Hypoplasia of the thyroid gland.

Therapy performed: MTX 12.5 mg 1 time/week, folic acid, Actemra 200 mg 1 time/4 weeks, voltaren, essentiale, bicillin-5.

Every month, the child was examined and treated with GEBD (Actemra) at the Mariupol Territorial Medical Association. Despite the lack of laboratory activity, there were complaints and signs of joint synovitis during ultrasound. Consulted at the Institute for Children and Adolescents Health Care of the National Academy of Medical Sciences of Ukraine, Kharkiv, it was recommended from 23.04.2019 to change GEBD from Actemra to Humira 20 mg once every 2 weeks, from 22.11.2019 the introduction of diprospan 0.5 mL in both ankle joints. In December 2019, there were complaints of morning stiffness for up to 30 minutes, pain in the joints, lameness, ESR – 31 mm/h, CRP – 29.04 mg/L. In June 2021, the complaints persisted, ESR – 19 mm/h, CRP – 5.82 mg/L, A-CCP <8 units/mL (normal – up to 17 IU/mL), modified citrullinated vimentin antibody (anti-MSV), IgG – 74.21 IU/mL (normal – 20 IU/mL), ANA <1:100, IL-6 – 20.97 pg/mL; ultrasound – signs of exudative synovitis of the knee, shin, hip, elbow joints, interphalangeal joints of the hands.

In connection with the active hostilities, the girl was evacuated from Mariupol, hospitalized in April 2022 in Kyiv the Institute of Pediatrics, Obstetrics and Gynecology of the National Academy of Medical Sciences of Ukraine for examination and correction of therapy. Prescribed: GCS – solu-medrol 40 mg for 6 days, then metipred 20 mg/day; MTX 12.5 mg/week, folic acid, adalimumab 40 mg/for 2 weeks. But there was no improvement in the girl's condition. MTX therapy was changed to leflunomide 10 mg/day, actemra, humira were changed to the Janus kinase inhibitor Xeljanz (tofacitinib) 5 mg/2 times/day. The girl's condition improved a month after the start of tofacitinib therapy.

The peculiarity of clinical case No. 3 is the presence of a persistent course in a child with a systemic variant of JIA, continuous progression of the disease, with multiple lesions of the joints and the development of contractures, as well as the presence of an unfavourable prognosis signs, such as lesions of the cervical spine, maxillary and hip joints, and the presence of radiological signs of joint damage. A peculiarity of the case is the simultaneous significant increase of IL-6 and TNF-α. Repeated correction and changes in therapy did not lead to clinical and laboratory remission. The disease progressed slowly. And only the prescription of the Janus kinase inhibitor Xeljanz (tofacitinib), even for one month, led to an improvement in the child's condition.

Discussion

Systemic JIA is a rare variant of the disease in children. Analysis of the presented study and analysis of clinical cases showed that sJIA is a severe and aggressive disease with an unfavourable prognosis. The systemic variant of the disease was diagnosed in 8 out of 88 patients with JIA (9.1%). Despite its low frequency among other variants of the JIA course, many problems arise in the diagnosis and selection of effective therapy.

Our observations proved that the diagnosis of sJIA is established quite late, half of the patients were initially admitted to the infectious disease department, the diagnosis of sJIA was established from 1 to 8 months after the onset of the disease. A variety of clinical symptoms, sometimes not specific, often leads to a late diagnosis of sJIA. Clinical manifestations of sJIA corresponded to literature data (Lee & Schneider, 2018; Albaker, 2020; Pawlocik et al., 2023). The onset of the disease in our patients, as in literature data (Bogmat & Shevchenko, 2017; Boiko, 2019; Koniushevska et al., 2022), was manifested by acute, hectic fever, skin syndrome, lymphadenopathy, polyserositis, and hepato- and splenomegaly, all children had a high level of laboratory activity of the disease, only one girl had a subacute onset of the disease.

The majority of the patients (6 out of 8) had sJIA with active systemic manifestations and varying degrees of arthritis activity, with a persistent course and formation of chronic polyarthritis. In one patient, sJIA proceeded as a classic allergoseptic variant of the disease, with a predominance of pronounced active systemic manifestations at the onset of the disease. Classic Still's syndrome with moderate fever, with limited visceritis, but with pronounced polyarthritis was observed in one child. In one more patient (of course, the girl was not included in the group of children with sJIA), the nosological affiliation could not be accurately determined, and the arthritis remained undifferentiated.

According to the ILAR criteria, the presence of arthritis is one of the conditions for establishing a diagnosis of sJIA (Ringold et al., 2013; Albaker, 2020; Onel et al., 2022). However, during our observation, 3 out of 8 patients had a delayed joint syndrome that occurred several months after the onset of systemic manifestations. Therefore, such children in the early stages of sJIA without having 6-week arthritis may not meet the ILAR criteria, which is also indicated by many authors (Kimura et al., 2017; Hinze et al., 2018; Smolewska et al., 2021).

In this regard, it is possible to apply the Yamaguti criteria, which consider the presence of arthritis not mandatory for the diagnosis of sJIA, this contributes to the early diagnosis of sJIA (Martini et al., 2019; Albaker, 2020; Koniushevska et al., 2022).

But over time, classic structural changes in the joints were found in all patients of the study group. 1/3 of the patients had X-ray stage III with widespread osteoporosis, pronounced bone-cartilage destruction, which may be related to the persistent course and activity of the disease, which persisted for years.

It should be noted that patients with various variants of JIA may have eye damage (Boiko, 2019; Albaker, 2020). A feature of the development and course of uveitis is the delayed development of eye damage from joint syndrome. At the same time, the term of uveitis manifestation can vary many years after the development of joint syndrome, or uveitis can occur many years before the development of joint syndrome.

Uveitis rarely develops in sJIA (Albaker, 2020), but in our clinical case, uveitis occurred in a boy with sJIA with active systemic manifestations (allergoseptic variant) 13 years after the onset of the disease, was asymptomatic, with outwardly inconspicuous manifestations, according to the type of chronic anterior uveitis. This boy was ANA positive for the disease. Untimely diagnosis and treatment of sJIA can lead to serious complications. One child out of the 8 patients with sJIA developed a serious life-threatening condition – MAS.

Treatment should be individualized taking into account the severity of clinical manifestations, the degree of joint damage, the presence of relapses in the anamnesis, an adequate response to treatment, which will permit the correct selection of the most effective therapy regimen. It is recommended to start treatment as early as possible to achieve early control of the disease and avoid early disability of the child due to destructive joint changes (Ravelli et al., 2018; Albaker, 2020). Many studies have shown that the later the diagnosis of sJIA is established, the more inadequate the response to treatment will be (Albaker, 2020; Vitale et al., 2020).

All children with sJIA were treated with GCS therapy (pulse therapy with solu-medrol followed by a maintenance dose of GCS). Unfortunately, the duration of taking GCS exceeded 2–3 years, hormone dependence was noted in ¾ of the patients. The most serious undesirable phenomenon of the GCS prescription was the development of a severe osteopenic syndrome in a teenager. In our study, MTX was administered to all children with sJIA in combination with glucocorticosteroid or biologic therapy, consistent with literature data (Hinze et al., 2018; Boiko, 2019).

Biological therapy was prescribed late, mainly due to the late diagnosis of the disease. The study proved the efficacy and safety of prescribing tocilizumab in children with sJIA. In patients with refractory sJIA, the use of JAK inhibitors (Tofacitinib) has shown positive results (Huang et al., 2019; Albaker, 2020; Zhao et al., 2020; Pawlocik et al., 2023). This was also confirmed in our study, in a child with a persistent course of sJIA only after the prescription of tofacitinib for a month, did improvement of the condition occur for the first time.

Conclusion

Thus, in this difficult and multifaceted pathology, which is JIA and sJIA, unsolved issues remain. At present, it is impossible to determine the optimal approaches to the therapy of sJIA. The global trend towards earlier prescribing of GEBD in sJIA provides an opportunity to refrain from long-term use of GCS or their prescription. However, no algorithm has been developed for the prescription of GEBD in the debut of sJIA, taking into account various initial characteristics of the patient: demographic, clinical, and laboratory.

Knowledge and sufficient clinical experience in the issues of clinical polymorphism of the onset and course of sJIA will help pediatricians, children's rheumatologists in early diagnosis, will provide an opportunity to verify the disease more quickly, prescribe effective therapy in a timely manner, choose a drug and an individual treatment regimen for each sick child, which will prevent the development of complications, predict and influence the prognosis and the course of the disease, which will significantly increase the probability of achieving remission and improve the quality of life of patients.

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