Systemic juvenile idiopathic arthritis in the pediatric practice of Donetsk region


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Introduction

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of diseases of unclear etiology, characterized by a complex autoimmune 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; Bogmut & 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; Oshlyanska & 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 depend 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-
nifizations, which, on the one hand, is characterized by the severity of the general inflammatory response, bright polynodcardia, 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; Korunshvskaya 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; Korunshvskaya 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, oncology, 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 (Hinz et al., 2018; Belyaeva 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 (65%) at the onset of the disease were hospitalized in non-specialist departments, and only 15% – in cardiorheumatic departments (Alekseeva et al., 2015; Baranov & Alekseeva, 2016; Boiko, 2019).

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 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 polyyclic 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 limitations of the movement and self-care possibility, physical, mental, and social maladaptation of children and reduces their quality of life (Salagina, 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 facilitat-
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”. Oft’em, 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 hands, 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 monocytecous 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 hepatitis 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 38.5°C. 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 hepatosplenomegaly. 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 articulargia 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 (CHAC 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 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 10⁹/L, n = 8) with a neutrophil shift to the left (up to 10–15% of stab neutrophils leukocytes), thrombocytosis (400–560 x 10⁹/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.
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 89 µg/mL (normal to 7 µg/mL), but the level of IL-1 was normal. Along with a significant increase in the level of IL-6 (168 µg/mL), in 1 child, a significant increase in the level of TNF-α was simultaneously increased to 25.5 µg/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 periarthritis 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.

### Table 1

<table>
<thead>
<tr>
<th>Indices</th>
<th>Number of patients with JIA n = 88</th>
<th>P, %</th>
<th>Number of patients with JIA, n = 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girls</td>
<td>60</td>
<td>68.2</td>
<td>7</td>
</tr>
<tr>
<td>Boys</td>
<td>28</td>
<td>31.8</td>
<td>1</td>
</tr>
<tr>
<td>Ratio</td>
<td>2:1</td>
<td>2:1</td>
<td>7:1</td>
</tr>
<tr>
<td>Urban dwellers</td>
<td>73</td>
<td>83.0</td>
<td>7</td>
</tr>
<tr>
<td>Rural dwellers</td>
<td>15</td>
<td>17.0</td>
<td>1</td>
</tr>
<tr>
<td>Ratio</td>
<td>5:1</td>
<td>5:1</td>
<td>7:1</td>
</tr>
</tbody>
</table>

**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.
All children with sJIA received and are still receiving MTX at a dose of 15 mg/m²/week. The mean duration of MTX therapy was 48.8 ± 10.5 months.

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 cerebral 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 period of time. The use 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 paronychia, a severe osteopenic syndrome, 1 girl had empyema of the gall bladder, 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 JA, 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°C), 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 leucocytosis 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 – leucocytosis (12.8 x 10⁹/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), dipherela mine 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, autoaggregation 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), arthropit-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, plaquenil (hidroxicloroquina) 100 mg per day, firoxiparin for 10 days, dipyridamole, diclofenac, calcemia, aspirmak. Against the background of therapy, the
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 plaquenil were discontinued. In May 2005, after ARVI the child showed laboratory activity of the process: accelerated ESR to 21–25 mm/L, 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, gastric disturbances, rashes on the skin of the trunk and limbs, generalized weakness, and increased body temperature appeared. In the blood analysis: leukocytosis (17.7 × 10^9/L), neutrophilia (stab neutrophils – 28%, segmented neutrophils – 48%), accelerated ESR – 38 mm/L. 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°C, 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.

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 paronychia of toes I, II, III, ingrown nails. In the lungs, vesicular breathing, the boundaries of the heart were not expanded, the tones were rhythmic, ruffled, 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 – 2.06–2.37 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 lumbar spinal spine: signs of deforming spondylodiscosis, osteochondrosis of the lumbar spine with protrusion of the intervertebral discs L3–S1, Schnorrt's hernia of the locking plates of Th11–L4 vertebral. Osteogenon, calcium-D3-Nicomed, a reduced dose of metrol 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 paronychia 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 is no sign of local inflammation. Vesicular breathing in the lungs. The boundaries of the heart were not expanded, the tones were rhythmic, ruffled. The abdomen was soft, painless, the liver, spleen were not enlarged.

Examination: there was no laboratory activity of the process (ESR – 3 mm/h, CRP – negative). Rheumatoid factor – Fc-fragment of IgG autoantibody IgA (RF) – 0.12 (normal < 1.0); Fc-IgG fragment of IgA au-
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°C, 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, pronounced arthralgias occurred. Significant anemia and high laboratory activity were detected. From the anamnesis, it is known that in December 2004 she fell ill with ARVI and acute bronchitis. Two weeks after ARVI, pronounced arthralgias occurred. Significant anemia and high laboratory activity were detected.

Clinical diagnosis: Juvenile idiopathic arthritis, systemic variant (allergic-synergistic 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 gastroenteritis, incomplete clinical and laboratory remission; Chronic compensated tonsillar-laryngitis; Osteopenic syndrome. L5 retrothesis, deforming spondylolisthesis, osteochondrosis of the lumbar spine with protrusion of the intervertebral discs L3–S1, Schmorl's hernia of the locking plates of Th1–L4 vertebrae; Recurrent parainfluenza 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 pancreaticitis, exudative pericarditis, with dilatation of heart chambers, rhythm disturbance, saphenous- and venous extraostyloses, CF 2a), eye damage 13 years after the onset of the disease, development of a pronounced osteoporotic syndrome with severe damage to the spine.

Clinical diagnosis: Juvenile rheumatoid arthritis, systemic variant, polyarthritis, degree III of activity, seronegative, without eye damage, Ros stage I, F1.2. 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/m² (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 – sola-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 sola-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 contractions 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 × 10⁹/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 × 10¹²/L, Hb – 94 g/L, platelets – 280 × 10⁹/L, leukocytes – 11.5 × 10⁹/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) sorbitol-tolerating enzyme – 0.601 mg/ml (normal up to 8 mg/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 2.5 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 (methypred 12 mg/day) followed by a gradual decrease to 5 mg/day. Re-exacerbation occurred after 6 months (May, 2008) with symptoms of...
Pronounced hypercorticism, somatogenic dwarfism. Weight 46 kg, height 1.34 m. The range of motion is reduced in the hip joints (abduction) and radiocarpal joints (extension). Deformation of hands and feet. Gait was impaired.

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 Mi3 P3 M3 (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 growth zones of the main phalanges area are mostly open on the right.

Examinations:
1) 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 IIA 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, F1.2. 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, polyarthritis with limited visceritis, 3rd stage activity, seronegative, F1 2a. Severe anemia.

Complaints during hospitalization to the clinic: temperature rise to 38°C, 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 heparce, 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 curious. 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 10^12/L, platelets – 578 x 10^12/L, leukocytes – 11.5 x 10^9/L, eosinophils – 1%, stab neutrophils – 4%, segmented neutrophils – 57%, lymphocytes – 31%, monocytes – 7%, ESR – 55 mm/h; Blood analysis 02.06.2014: erythrocytes – 5.39 x 10^12/L, Hb – 97 g/L, reticulocytes – 0.0005 x 10^12/L, platelets – 540 x 10^12/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 > 36 U/L, ALT – 15 U/L, AST – 6 U/L, ALT – 15 U/L, blood sugar – 6.5 mmol/L; 4) ASLO – 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 pg/mL (normal – up to 8.2 pg/mL), IL-6 – 168 pg/mL (normal up to 7.0 pg/mL); 8) PCR: Chlamydia 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,
The necks were shortened, arthrosis changes in the roofs of the acetabulums with their shortening. Vanus deformity of the hips; 9) X-ray of both knee joints taken 28.06.2018: the joint spaces were narrowed, the cartilage loosers, the joint surfaces were smooth, the intercanal tubercules 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 gurus 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) ophthalmologist 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 reticuloendothelial system, heart, polyarthritus, 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, voluoret, essenciale, 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 – sola-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 98 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; Pavlović 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, polyarthritis, 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 allergic 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 visceralit, 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 (Kirmam et al., 2017; Hinze et al., 2018; Smolovelska 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 (allergic 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.

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 influenc the prognoz 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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References


