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REACTIVE ARTHRITIS IN THE PEDIATRIC PRACTICE OF THE DONETSK REGION

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The article considers the features of reactive arthritis course in children. The results of a retrospective study of 482 children with reactive arthritis are presented. Most often, reactive arthritis was diagnosed in pre-school children. In more than 27 % of cases, children have a history of acute respiratory infections, in 69.5 % of cases the trigger is not determined. It was found that in most patients the disease had acute character. Among the clinical manifestations the most common lesions of the hip and knee joints were of monoarticular type, children did not have high levels of laboratory activity. Relapses of the disease are not excluded.

Key words: reactive arthritis, children, clinical picture, diagnosis, treatment.

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РЕАКТИВНИЙ АРТРИТ У ПРАКТИЦІ ПЕДІАТРА ДОНЕЦЬКОГО РЕГІОНУ

У статті розглядаються особливості перебігу реактивного артриту у дітей. Наведено результати ретроспективного дослідження 482 дітей з реактивним артритом. Найчастіше реактивний артрит діагностовано у дітей дошкільного віку. Більш ніж 27 % випадків у дітей в анамнезі виявлено гострі респіраторні інфекції, у 69,5 % випадках тригер не встановлено. У більшості пацієнтів захворювання мало гострий характер. Серед клінічних проявів найчастіше зустрічалися ураження кульшових та колінних суглобів за моноартикулярним типом, діти не мали високого рівня лабораторної активності. Не виключені рецидиви захворювання.

Ключові слова: реактивний артрит, діти, клінічна картина, діагностика, лікування.

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In the structure of joint pathology in children, reactive arthritis (ReA) is from 8 to 56 % [5, 6]. The term "reactive arthritis", code M02 according to ICD 10, refers to aseptic, non-purulent inflammation of the joints that develops as a result of immune disorders and occurs in children during or 1–4 weeks after an infectious disease [2, 14].

Until now, the pathogenesis of ReA remains incompletely understood [8, 9]. ReA is thought to be an immune-mediated syndrome caused by an infection. Bacterial antigens from the site of penetration spread through the blood circulation into the synovial fluid and joints, and cause their inflammation [8, 12]. T lymphocytes are also activated and inflammatory cytokines are released, which also leads to synovial inflammation. The role of the intestinal microbiome in the pathogenesis of ReA is indicated in literary sources [6, 8, 14]. The role of HLA B27 in the development of ReA is not fully understood [1, 8].

At the IV International Working Meeting on ReA (Berlin, 1999), a decision was made to consider the main etiological factors of postenterocolitic ReA to be Yersinia, Salmonella, Shigella, and Helicobacter; urogenous – chlamydia, ureaplasma [8].

In childhood, respiratory agents (parvovirus B19, adenoviruses, Coxsackie viruses, herpesviruses) are the most frequent cause of ReA rather than urogenital or postenterocolitic agents [2, 8]. In 2020, ReA was first described in children with COVID 19 [10, 13]. In most children with ReA, the etiology is unknown [8].

The clinical features of ReA in children include: the acute nature of the joint syndrome – acute pain, swelling, temperature changes over the joint; the joints of the lower extremities (knee, hip) are more often affected, the characteristic development of oligo or monoarthritis; relapses of the disease are possible [2, 3, 11].

Until now, generally accepted diagnostic criteria for ReA have not been developed, and therefore the diagnosis of ReA, especially in children, is made clinically, based on history, physical examination, and thanks to ultrasound of the joints [7, 8]. The criteria of the American Rheumatology Association, the

Berlin criteria (1999) [8, 12], which are aimed at adult patients, are still used for the diagnosis of ReA [3]. There is no test to confirm the diagnosis of ReA [8, 14].

There are currently no generally accepted recommendations for the treatment of ReA [8]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first line of treatment for ReA [4, 8].

Local therapy for ReA includes intra-articular injection of glucocorticosteroids (GCS) [4, 8, 9], however, it is used extremely rarely in children [8]. Systemic use of GCS in children is not recommended [4, 8].

Until now, the issue of the antibiotic therapy efficacy (ABT) in ReA remains open [4, 8]. ABT is effective in PSReA and in chlamydia-induced ReA. Many questions remain about the benefit of antibiotic prophylaxis in PSReA and its efficacy in preventing the development of late carditis [9].

With timely diagnosis and treatment, 50–80 % of children with ReA pass without a trace. However, a chronic course of the disease and even transformation of ReA into JIA is possible [5, 11, 14].

The purpose of the study was to identify the clinical features of the onset and course of reactive arthritis in children in the ecologically disadvantaged Donetsk region.

Materials and methods. The research was performed 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 research. From January 2015 to February 2022, 482 children with ReA aged 11 months to 17 years who lived in the ecologically disadvantaged industrial Donetsk region and were treated in the Mariupol Territorial Medical Association of Child and Women's Health, Ukraine.

Patients with ReA were divided into groups according by age. ReA occurred more often in preschool age, the onset of the disease from 1 year to 6 years was in 248 sick children (51.5±2.3 %, $p<0.05$), before 1-year ReA was detected only in 1 child aged 11 months. 111 children (23.0±1.9 %) were diagnosed with ReA in the younger school group of 6–10-year-old, 122 children (25.3±2.0 %) were in the upper school group from 10–17 years old.

The diagnosis of ReA was verified according to the ReA criteria of the American Association of Rheumatology, Berlin criteria (1999) [13]. In addition to traditional laboratory parameters (blood analysis, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), urine analysis, stool analysis for helminths), an immunological study was performed, which included the study of rheumatoid factor (RF), antinuclear antibodies – ANA, antibodies to giardia (IgM, IgG), antibodies to chlamydia, mycoplasma, yersinia, ureaplasma, cytomegalovirus (CMV), Epstein-Barr virus (EBV), antistreptolysin O (ASL-O), bacterial culture from the nasopharynx for streptococcus, smears from the nasopharynx and oropharynx – to detect the DNA of microorganisms (PCR – Chlamydia pneumoniae, Mycoplasma pneumoniae, EBV, CMV).

Among the instrumental methods, radiological, ultrasound (ultrasound of the joints, abdominal organs, heart) and ECG were used. Consultation of an ophthalmologist, orthopedist-traumatologist, phthisiologist.

Mean values (M) and confidence interval for mean (CI – confidence interval for mean) were calculated. The difference was considered statistically significant at $p<0.05$.

Results of the study and their discussion. The mean age of ReA debut was 8.0±0.3 years. ReA occurred more often in boys (in 292 boys, 60.6±2.2 %) than in girls (in 190 girls, 39.4±2.2 %). Children who lived in the city were 14.5 times more likely to suffer from ReA than children who lived in the village (respectively, 451/31 children, 93.6/6.4 %, $p<0.05$). Family anamnesis related to the locomotor system was not burdened in any child.

The disease was preceded by acute respiratory viral infections (ARVI) in 130 patients (27.0±2.0 %), acute intestinal infections (AII) in 2 children (0.4±0.3 %), and in 2 children (0.4±0.3 %) ReA developed after the infectious mononucleosis (children were examined and treated for AII and infectious mononucleosis in the children's department of the Medical Center No. 4 in Mariupol), streptococcal infection (carriage) was detected in 8 patients (1.7±0.6 %), giardiasis – in 5 patients (1.0±0.5 %), but most often the factor was not established – 335 (69.5±2.1 %, $p<0.05$) (Table 1).

On average, the diagnosis of ReA was established 4.1±0.3 days after the onset of the disease. In the foreground in the clinical picture, the articular lesion stood out. All children with ReA had an acute onset of the disease (100 %, $p<0.05$). Children were bothered by sharp pain during movement, restriction of movement, edema, swelling, and changes in joint temperature. Acute pain, changes in joint temperature were present in all patients (100 %, $p<0.05$). Most patients had moderate swelling of the joint (395 children,

82.0±1.8 %, p<0.05). Morning stiffness was defined as very short-term in half of the patients (241 children, 50.0±2.3 %), but there was no pronounced long-term morning stiffness in any patient (p<0.05).

Table 1

Demographic and clinical characteristics of patients with ReA

Index	Number of ReA patients N=482	P %
Girls	190	39.4
Boys	292	60.6
Ratio B:G	1.5:1	-
Urban residents	451	94.0
Rural residents	31	6.0
Ratio Ur:Rr	14.5:1	-
Disease was preceded: ARVI	130	27.0
factor not determined	335	69.5
AII	2	0.4
Infectious mononucleosis	2	0.4
streptococcal infection (carriage)	8	1.7
Giardiasis	5	1.0
Mean number of active joints	1.3±0.1.	-
Number of affected joints: 1 joint	395	82.0
2–4 joints	74	15.3
5 and more joints	13	2.7
Joints affected the most frequently:		
Knee	173	35.9
Hip joints	246	51.0
Ankle joints	40	8.3
Radiocarpal joints	12	2.5
Temporomandibular joints	-	-
Cervical spine	-	-
Elbow joints	-	-
Shoulder joints	3	0.6
Interphalangeal joints of the hand	8	1.7
Small joints of the foot	-	-
Fever: hectic	-	-
moderate	70	14.5
without fever	412	85.5
Mean fever duration, days	3.0±0.25	-
Clinical laboratory remision archieved, days	10.4±0.28	-
Number of children with disease relapses	41	8.5
1 relapse	28	68.0
2 relapses	13	32.0
During 6 months of the disease	38	92.7
Mean age of ReA onset, years	8.0±0.3	-

Any joint can be a target of ReA, however, most often, at the onset of the disease, the joints of the lower extremities with a characteristic asymmetry of the joint syndrome were involved in the inflammatory process (445 children, 92.3±1.2 %, p<0.05), mainly monoarthritis was observed, which was detected in 395 children (82.0 ±1.8 %), 74 children had oligoarthritis (15.3±1.6 %), and only 13 children had polyarthritis (2.7±0.7 %). Hip (246 children, 51.0±2.3 %) and knee joints (173 children, 35.9±2.2 %) were most often affected, ankles (40 children, 8.3±1.3 %) and carpal joints (12 children, 2.5±0.7 %) were much less frequently affected), very rarely – small joints of the hand and shoulder joints. 206 children of preschool age (83.1±2.4 %) and 40 children of primary school age (36±4.6 %) had lesions of the hip joins; there were no lesions of the hip joins in children of high school age (p<0.05). The mean number of active joints at the onset of the disease was 1.3±0.1. There was no damage to the cervical spine, temporomandibular joints, elbow joints, small joints of foot (p<0.05). Not a single child hat enthesitis, dactylitis, spondylitis and sacroiliitis (p <0.05).

After ARVI, ReA developed on average after 7.3±0.5 days, but there was a small number of children (8 children out of 130, 6.2±2.1 %) when ReA developed on the background of ARVI. After AII, infectious mononucleosis, ReA developed after 3–4 weeks (28.3±3.8 days) from the onset of the infectious disease.

At the onset of the disease, almost all children with ReA (99.8±0.2 %, p<0.05) did not have a high level of disease activity. The disease occurred with moderate fever in 70 patients (14.5±1.6 %) from 37.1°C to 38.0°C (on average 37.6±0.1°C), the duration of fever was 3.0±0.25 days. Most children with ReA did

not have fever (412 children, 85.5±1.6 %, p<0.05). Not a single child had lymphadenopathy, hepatomegaly, splenomegaly, there was no damage to internal organs, there was no damage to the eyes (p<0.05).

Only 1 child, a 6-year-old boy, had high activity of the inflammatory process at the onset of the disease. Against the background of a fever of 38°C, he had severe pain in the hip, knee joints, and then in the shoulder joints, blood tests revealed leukocytosis – 11.6 G/l, ESR – 30 mm/h, CRP – 39.70 mg/l.

Clinical blood analysis in most children with ReA (433 children, 90.0±1.4 %, p<0.05) was without deviations from the norm. A slight increase in ESR from 15 to 20 mm/h, on average 17.0±0.59 mm/h, and leukocytosis from 10 G/l to 20 G/l, on average 12.3±0.51 G/l, was found in 49 patients (10.0±1.4 %). The majority did not have an increase in acute phase indices (401 children, 83.2±1.7 %, p<0.05). Thus, CRP was slightly increased (5.0–15.0 mg/l) only in 80 children (16.6±1.7 %). Most often, ESR and CRP were within the physiological norm. RF, ANA were negative (100 %, p<0.05).

All children were swabbed from the nasopharynx and oropharynx to detect the DNA of microorganisms (PCR – Chlamydia pneumoniae, Mycoplasma pneumoniae, viruses – EBV, CMV). In all children with ReA, PCR results were negative (100 %, p<0.05).

Streptococcal infection was detected in 8 patients (1.7±0.6 %). The titer of ASL-O was increased in 27 patients (5.6±1.0 %), but the titer of ASL-O was increased by 2–3 times in 8 patients (1.7±0.6 %), in whom streptococci were detected in bacterial culture from the nasopharynx. In the anamnesis of these children, there is evidence of the presence of tonsillitis and frequent sore throats. They were all school-aged children.

If giardiasis was suspected, a fecal analysis for giardia cysts, a blood tests for IgM, IgG antibodies to giardia were performed. Giardiasis was detected in 5 patients (1.0±0.5 %). Four children were examined and treated for laboratory-confirmed AII (2 children, 0.4±0.3 %) and infectious mononucleosis (2 children, 0.4±0.3 %) in the Medical Center No. 4 children's department in Mariupol.

But most often the etiological factor was not established – in 335 children (69.5±2.1 %, p<0.05), it was not possible to detect the presence of infection from the anamnesis data and during laboratory examination in these children.

Analysis of the X-ray picture of the disease showed that no structural changes in the joints were found in all patients (100 %, p<0.05). In all patients, the inflammatory process in the joints was confirmed by ultrasound of the joints. Signs of synovitis were detected at the onset of ReA in all patients: swelling of peri-articular tissues, thickening of the synovial membrane, accumulation of synovial fluid in the joint cavity (100 %, p<0.05).

Immediately after the diagnosis of ReA, all patients were prescribed therapy. All children with ReA received NSAIDs (100 %, p<0.05). Nurofen was most often used among NSAIDs, and diclofenac was prescribed for children older than 8 years. The duration of NSAID therapy was up to 2–4 weeks, on average 10.3±0.3 days. Systemic use of GCS was not performed in children with ReA, and intra-articular administration of GCS was not performed either.

Depending on the causative agent of the infection, the presence of chronic infection’s foci, the clinical course, the presence of leukocytosis, increased ESR, CRP, increased ASL-O, children with ReA were prescribed antibiotics. 296 children with ReA received ABT (61.4±2.2 %), the most common ABT was macrolides – in 262 children (88.5±1.9 %) (azithromycin, clarithromycin, roxithromycin, spiramycin). Penicillins (augmentin, bicillin 5) and cephalosporins (ceftazidime, cefoperazone) were received by children with streptococcal infection, AII (34 children (11.5±1.9 %)). Children with ReA (5 children, 1.0±0.5 %) with intestinal giardiasis received the Macmiror (nifuratel) drug. In the absence of the Macmiror prescription, these children showed relapses of joint syndrome. All children with ReA (100 %) received the herbal preparation Incena (Austria) with analgesic, anti-inflammatory and anti-edematous effects.

Against the background of therapy, significant positive dynamics of the disease were noted, joint syndrome was relieved and laboratory parameters were normalized. Clinical laboratory remission was achieved in an average of 10.4±0.28 days, from 7 days to 1 month, not taking into account that a small number of children had relapses of the disease. The duration of inpatient treatment of children with ReA ranged from 7 to 14 days (7.6±0.25 days). Relapses of the disease were observed in 41 children with ReA (8.5±1.3 %). Almost all children with ReA had relapses in the first 6 months of the disease (38 children, 92.7±4.1 %). 28 patients had one relapse of the disease (68.3±7.3 % of the number of children with relapses of the disease), 2 relapses – 13 patients (31.7±7.3 %). The presence of ReA relapses depended on the child's age. These were children of preschool age only (p<0.05).

6 (1.2±0.5 %) children with ReA were diagnosed with JIA. At the onset of the disease, these children had a fever of 37.8–38.0ºC, leukocytosis of 15.0–20.0 G/l, ESR from 15 to 20 mm/h, CRP from 12.0 to 15.0 mg/l. The children did not respond to NSAIDs and ABT for 4 weeks, persistent joint syndrome persisted, a re-examination revealed an increase in ESR and CRP, and a high titer of ANA (1:300 – 1:1200).

In our study, 482 children with ReA were under supervision, among the patients there was a predominance of children of preschool age (248 children, 51.5 %). According to Klimenko V.A. et al. also found that children of preschool age most often suffered from ReA. But according to Senatorova H.S. et al., almost half of the patients (46.7 %) were children of high school age. Some authors note that gender does not play a role in the development of ReA, but others indicate that ReA occurs more often in girls (60 %) [3, 5], while others note, boys predominated among patients (55 %) [6, 11]. According to our data, ReA occurred by 1.5 times more often in boys.

Authors Lebets I.S., Panko N.O., and Senatorova H.S. et al. found that in a third (33.3–39.5 %) of children, the onset of arthritis was preceded by ARVI, in half (53.3 %) no predisposing factor was identified, this is consistent with our data – 27 % were preceded by respiratory diseases, had none of any what were the triggers in the anamnesis 69.5 % [3, 5].

The analysis of the data obtained by us shows that all children with ReA had an acute onset of the disease with pronounced joint syndrome, which is also confirmed in the literature [2, 3, 5]. According to the published studies of Lebets I.S., Panko N.O., Senatorova H.S. et al., the typical manifestation of joint syndrome in children is asymmetric monoarthritis (56.7–85.19 %) or oligoarthritis (14.81–40 %) of the lower extremities [3, 5]. According to Klimenko V.A. et al., Tverdohleb T.A. monoarthritis develops more often in preschool children, and oligoarthritis occurs in middle and older age groups [2, 6]. According to our observations, the joints of the lower extremities were involved into the inflammatory process in all age groups (445 children, 92.3 %), monoarthritis was mainly observed (395 children, 82.0 %), oligoarthritis was observed in 74 children (15.3 %). The results of our study show that hip joints (246 children, 51.0 %) and knee joints (173 children, 35.9 %) were most often affected. 206 children of preschool age (83.1 %) and 40 children of primary school age (36 %) had lesions of the hip joints; there were no lesions of the hip joints in children of high school age. Knee joints were affected in children of all age groups. Klimenko V.A. et al. found that hip (41.7 %) and knee joints (38.3 %) lesions predominated in preschool children, and 71 % of high school children had arthritis of the knee joints [2].

The analysis of the data obtained by us shows that at the onset of the disease, almost all children with ReA (99.8 %) did not have a high level of disease activity. The disease occurred with moderate fever only in 14.5 % of patients. The majority of children with ReA did not have fever (412 children, 85.5 %). Not a single child had damage to internal organs, damage to the eyes. Clinical blood analysis in the majority of children with ReA (433 children, 90 %) was without deviations from the norm. A slight increase in ESR on average of 17.0±0.59 mm/h and leukocytosis on average of 12.3±0.51 G/l were only detected in 49 patients (10 %). Most children with ReA did not have an increase in acute phase indices (401 children, 83.2 %). CRP was slightly increased from 5.0 to 15.0 mg/l in 80 children (16.6 %). Most often, the indices of ESR and CRP were within the physiological norm, which coincides with the data of the literature [3].

X-ray examination revealed no structural changes in the joints (100 %). The inflammatory process in the joints is confirmed by ultrasound of the joints [5, 7]. We found signs of synovitis at the onset of ReA in all patients (100 %). In the studies of Alamdaran S.A. et al. indicated that a small volume of effusion in the joint is less than 0.5 cm^3, low activity of the disease (leukocytes less than 12 G/l, ESR less than 40 mm/h, CRP less than 15 mg/l, absence of high fever) permits to distinguish ReA from of septic arthritis, which coincides with our studies [7].

According to our observations, relapses of the disease were observed in 8.5 % of children with ReA in preschool age. Authors Klimenko V.A. et al., Gupta R. et al. describe relapses of the disease in a quarter of children with ReA (25–27 %) [2, 11]. According to Klimenko V.A. et al. recurrent course of ReA was more common in preschool children (42 %) [2]. We also established that only 1.2 % of children with ReA were diagnosed with JIA. These children had a fever, persisting joint syndrome, did not respond to therapy for 4 weeks, leukocytosis more than 20.0 G/L, ESR was more than 20 mm/h, CRP – more than 15.0 mg/L, upon re-examination an increase in ESR and CRP was found, appeared high ANA titer.

Conclusions

1. A feature of ReA in children in the Donetsk region is the predominance of the disease in children of preschool age (51.5 %). The disease was preceded in 27 % of children by respiratory diseases, in 69.5 % the trigger was not established.

2. The analysis of the ReA clinical course of showed that all patients had an acute onset of the disease, mainly monoarthritis was observed (82 %), hip (51 %) and knee joints (35.9 %) were most often affected.

3. At the onset of the disease, almost all children with ReA (99.8 %) did not have a high level of disease activity. Clinical blood analysis in 90 % of children with ReA was without deviations from the norm. A slight increase in ESR and leukocytosis were in 10 %. In the majority, there was no increase in acute phase indices (83.2 %).

4. During the ultrasound of the joints, signs of synovitis were detected in all children with ReA (100 %).

5. The majority of ReA in children with timely diagnosis and therapy ends in recovery. Only 8.5 % of children with ReA of preschool age had relapses of the disease. 1.2 % of children with ReA were diagnosed with JIA. It is necessary to pay attention to persistent joint syndrome, fever more than 38.5ºC, lack of effect from therapy for 4 weeks, leukocytosis more than 20.0 G/L, high ESR more than 20 mm/h, CRP more than 15.0 mg/L, positive ANA titer, it may be grounds for repeated differential diagnosis, repeated laboratory examination to rule out or verify JIA in a timely manner, as early as possible.

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