Introduction

Acute osteomyelitis is an infection of bone and bone marrow caused by pyogenic bacteria. In children, particularly at neonatal age, the bacteria reach the bone usually through the bloodstream, hence the name acute hematogenous osteomyelitis (AHO) [1]. Septic arthritis (SA) is a pyogenic infection of the joint. These two conditions often occur simultaneously, especially in the youngest age group – more than half of infants with septic arthritis also have associated osteomyelitis [2]; thus, they are commonly referred to as "osteoarthritis". AHO can affect any bone of the skeleton, but both AHO and SA usually occur in long bones, especially in the lower extremities. Proximal metaphysis of femur and tibia are most often affected, while proximal metaphysis of humerus is rarely a site of AHO and SA [1]. Acute hematogenous osteomyelitis and septic arthritis are rare conditions - their prevalence is 1-3 cases per a thousand hospital admissions in the neonates [3]. Their clinical significance lies in the fact that they can result in permanent disability or even fatal outcome unless early recognized and adequately and promptly treated.

The aim of this paper is to present two premature newborns with rare localization of osteoarthritis – the humerus and shoulder joint, as well as to point to the modern diagnostic and therapeutic approach to this disease.

Case reports

CASE 1: a eutrophic premature newborn, born after 34 weeks of gestation, weighing 1730g at birth. The newborn was well, with no significant clinical and laboratory findings in the first 21 days. On the 22nd day of life, the swelling of the left shoulder occurred, accompanied by the absence of spontaneous movements of the left arm and painful crying with passive left arm motion (Figure 1).

The results of sepsis screen demonstrated the value of C-reactive protein (CRP) of 24 mg/l, white blood cells (WBC) 13.1x10^9/l with 57% neutrophils, fibrinogen 4.2 g/l. Immediately after the collection of biological material for bacteriological examination, intravenous antibiotic therapy with amikacin® and clindamycin® was introduced. Escherichia coli, which had been isolated by the bacteriological analysis of blood specimen, showed sensitivity only to carbapenems (imipenem® and meropenem®). According to this result, antimicrobial therapy was adjusted by introducing meropenem®. The bacteriological and biochemical findings of cerebrospinal fluid and urine were normal. The workup of osteoarthritis of the left shoulder was performed simultaneously with neonatal sepsis screen. Shoulder joint aspiration was done under ultrasound guidance and sparse...
amount of turbid fluid was obtained, whose bacteriological analysis yielded a negative result. The radiography of the left humero-scapular joint revealed a minimal fragmentation of proximal humerus. Meropenem® therapy lasted for 4 weeks. On the very next day after the introduction of appropriate antibiotic therapy, a decline in the value of acute phase reactants of inflammation was observed; 3 days later they were within the normal range. The control blood cultures were negative. After 20 days of gradual recovery, the infant showed a full range of motion in his left arm. The control radiography, performed a month after the bone-joint infection had begun, showed a still visible periosteal reaction of the left humerus, but the humeral head contours were smooth and regular. The follow-up showed a complete recovery - appropriate, symmetrical growth of both arms, with a full range of motion in his left shoulder.

CASE 2: a premature male infant, born after 36 gestational weeks, weighing 2100g at birth (below 10 percentile). He showed signs of respiratory distress at birth, and was on non-invasive respiratory support - nasal continuous positive alveolar pressure (CPAP). Since it was observed that CRP increased to 33 mg/l on the fifth day of life, intravenous antibiotic therapy - ampicillin® and gentamicin® - was started. Despite antibiotic therapy, there was a further increase in acute phase reactants of inflammation (CRP 85 mg/l, WBC 25x10⁹/l), and the treatment was adjusted by introducing meropenem® and vancomycin®, with intravenously administered immunoglobulins. Before the changes of antibiotics were introduced, the cultures had been taken for bacteriological analysis. The blood culture was positive - Staphylococcus aureus was isolated, which was sensitive to both antibiotics included later. Cerebrospinal fluid and urine culture were negative. Staphylococcus aureus was also isolated from the nose and throat swabs. Chest radiography showed the presence of alveolar infiltrates with clearly limited thin-walled cystic shadow of 15 mm in diameter and 3 mm thick wall, located in the projection of the middle, right lung lobe, which, along with clinical, laboratory and bacteriological analysis, corresponded to the existence of staphylococcal pneumonia with pneumatocele. The respiratory status of the newborn gradually improved with antibiotic and supportive therapy of generalized and respiratory infections, and he started breathing spontaneously without respiratory support on the 9th day of life. However, throughout that period, he was in poor condition, with scarce spontaneous movements, and occasionally sub-febrile. C reactive protein was within the normal range from the 18th day of his life. Since then, the child’s general condition improved, with increasing spontaneous activity. On the 14th day of life, the swelling of the right shoulder was observed, accompanied by restricted active mobility of the right arm (which the child moved much less than the left arm) and pain at attempted passive motion of the right elbow and shoulder joint. Ultrasound and x-ray of the right shoulder showed deformity of the right humeral metaphysis (Figure 2).
A small amount of liquid was obtained by joint needle aspiration, whose bacteriological analysis was negative. Antibiotic therapy with meropenem and vancomycin was continued with subsequent gradual improvement in general condition of the child, and local findings in the right shoulder. The control radiograph made after 2 weeks showed rarefaction of proximal metaphysis of the right humerus, with periosteal reaction (Figure 3). At that point, the physical examination did not show oedema of the right shoulder any more, but there was still a reduced range of motion in the right shoulder joint accompanied by audible crackles. The total duration of intravenous antibiotic therapy (meropenem®, vancomycin®) was 4 weeks; amoxiclav (according to the antibiogram) was administered orally for 2 weeks thereafter. The X-ray control was made at the age of 2 months - rarefaction of right humerus metaphysis was still present, although considerably less visible than in the previous X-ray image (Figure 4).

As soon as the signs of active infection disappeared, physical treatment was initiated. On the subsequent outpatient controls, a reduced range of motion in the right shoulder joint was still present after 3 months.

Discussion

AHO and SA often occur simultaneously during the first 18 months of life, because of the continuous blood supply to the epiphysis and metaphysis present at that age [2]. AHO mostly affects well-vascularised metaphysis in the long bones. The terminal branches of metaphyseal arteries terminate in the network of capillary loops and venous sinusoid, where the blood flow is sluggish and the number of functional phagocytes low, thus making conditions suitable for the inoculation of bacteria and the development of infection exactly at these places. Bacterial septic emboli clog blood vessels and raise intraosseal pressure. As the result, ischemic bone necrosis occurs, which leads, with the progression of infection, to the formation of abscesses in the metaphysis [1]. The specific joint structure and vascular connections between metaphysis and epiphysis at the youngest age enable direct penetration of infection into the joint, with the resulting occurrence of SA [2]. The infection leads to the increased production of joint fluid rich in leukocytes, and due to the disintegration of leukocytes, proteolytic enzymes are released, which along with the pus, lead to the destruction of articular cartilage with the possibility of permanent damage to the major structures of the joint. This is especially evident at the neonatal and early infant age [4].

AHO primarily occurs in the femur and tibia, and rarely in the humerus. SA occurs in the hip joint in as many as 80% of cases in the youngest age groups [1], whereas its frequency in the shoulder joint is 3-5% [5]. In some long bones (proximal femur, proximal humerus, proximal radius and distal part of tibia), metaphysis is located within the articular capsule, so metaphyseal abscess can be drained into the joint causing concomitant SA [1].

A wide range of microorganisms can cause AHO. *Staphylococcus aureus* is the most common causa-
tive agent of AHO in all age groups [1,6,7]. Besides staphylococcus, group B streptococcus and gram-negative bacilli are frequently found at the neonatal age [2,6]. Since newborns, especially premature, are immunocompromised patients, one should always consider fungi as possible causative agents [8]. Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a cause of AHO in recent studies [3]. When it comes to septic arthritis, the most common causative organisms are very similar to those causing AHO (*Staphylococcus aureus*, group B streptococcus, coagulase-negative staphylococci, gram-negative bacilli), while in more recent studies *Kingella kingae* has emerged, especially in children younger than 2 years of age [1,8-10].

Symptoms and signs in infants with AHO and SA are rather nonspecific and can easily be overlooked. Since this is practically a septic condition at this age [4], clinical signs of generalized infection are manifest. The main clinical sign indicating the bone-joint infection is the absence of active mobility of the affected joint, the so-called pseudoparalysis, accompanied with painful crying at an attempted passive motion. There may be swelling and redness of the affected joint. A high degree of suspicion and careful observation of the newborn are essential for early diagnosis and subsequent successful treatment of AHO and SA. In the first reported case, the clinical features of generalized infection were sparse and the positive local findings with early appearance of symptoms and signs of the shoulder joint infection dominated. This led to the early diagnosis and timely treatment, with complete healing without damage to the anatomy and function of the affected joint. In addition to AHO and SA, our second patient had staphylococcal septicemia and pneumonia, which were accompanied by the severe general condition and respiratory symptoms dominating during the first stage of disease, and poorly marked signs and symptoms of osteoarthritis because of general adynamia. Therefore, the bone-joint infection was detected relatively late, and so the treatment was late with resultant damage to the joint function.

Diagnosis of AHO and/or SA, following the suspicion towards clinical findings, requires further investigations including plain radiography of the suspected joint as mandatory examination. In the early stage of disease, the soft tissue swelling is the only radiological finding, but this sign is often subtle and easily overlooked. Changes in bones are usually observed on standard radiographs only 10-16 days after the onset of infection [4]. The first radiographic sign of AHO is inhomogeneous rarefaction of bone density [1]. However, due to the absence of epiphyseal bone in newborns, this bone damage is not manifested on X-ray at neonatal age [4]. In addition to the soft tissue swelling, radiographs in the initial phase can show widened joint space and "hazy" appearance of the bone, with or without subluxation [11]. Bone deformation and disorders of bone ossification and growth can be seen in the subsequent course of the disease. Bone radiographs are important not only as a tool for excluding other diseases and conditions that must be considered in the differential diagnosis, but also for long-term monitoring of possible complications [11]. An indispensable part in the diagnosis of bone and joint infections are ultrasonography and joint aspiration. Ultrasonography is more useful during the initial stage of disease than X-ray, because radiographic changes occur late. In the hands of an experienced ultrasonographer, changes in acute osteomyelitis can be detected as early as 48 hours after the onset of infection [11]. Ultrasound can reveal the presence of the subperiostal pus and joint effusion. In addition, ultrasound serves as a guide for joint needle aspiration, which should be done under anesthesia. It is important to note that a negative aspiration does not exclude bone-joint infection [1]. All aspirated material should be sent to the laboratory and bacteriological examination. The presence of bacteria confirms the diagnosis of osteoarthritis. However, bacterial culture is negative in more than one third of cases, thus negative finding does not exclude infection [1,2]. Blood culture is positive in 30-50% of cases [1]. Bone scintigraphy is rarely needed for diagnosis of SA. It should be performed only in insufficiently clarified cases [12], as well as in the detection of multiple locations [1]. Computerized tomography and magnetic resonance imaging are also not used routinely in the diagnosis of osteoarthritis, but are reserved for the vague and/or complex cases [12].

The diagnosis of osteoarthritis is based on clinical findings, laboratory analysis, radiography and ultrasound examination with joint aspiration accompanied by laboratory and bacteriological examination of the obtained fluid and blood culture (with possible additional tests in rare cases), and should meet the following criteria: 1. clinical features - the presence of localized pain and lack of motion of the joint, local swelling and redness, 2. corresponding radiographic and/or ultrasound findings, 3. positive blood culture and/or culture of joint fluid [13]. All these diagnostic criteria were met in both cases reported in this paper.

AHO and SA therapy must be prompt, with aspiration and drainage of the affected joint and antibiotic therapy in appropriate, high-doses of sufficient duration. Antibiotic therapy should be started immediately after sampling the material for bacteriological analysis - empirical first, then according to sensitivity finding. Current epidemiological trends should be followed both in literature and in local environment since these data have important implications for selection of early empirical antimicrobial therapy [6]. At the neonatal age, a combination of penicilasa-resistant penicillin and aminoglycoside is recommended. If infection is acquired in hospital settings, methicillin-resistant *Staphylococcus aureus* (MRSA) should be taken into consideration. Clindamycin and vancomycin are the most reliable in such cases [8]. *Kingella kingae* is getting more and
more frequent cause in community-acquired bone-joint infection in all children younger than 2 years of age. This bacterium is sensitive to a wide range of antibiotics, including ampicillin, cephalosporins, aminoglycosides and semisynthetic penicillins [1]. The length of antibiotic therapy is dictated primarily by therapeutic response. Recent studies have shown a good outcome if intravenous antibiotic therapy is replaced by oral antibiotics as soon as laboratory indicators of infection have been normalized, which shortens the duration of in-hospital treatment and reduces complications associated with long-term venous route [14]. However, since osteoarthritis always represents a generalized infection at the neonatal age, prolonged intravenous antibiotic therapy is inevitable, lasting for a period of 2-6 weeks [15]. In addition to antibiotics, adequate drainage of the affected joint is mandatory - a procedure without which there is no cure of infection. In the case of an easily accessible joint (e.g. shoulder, elbow, knee), a needle aspiration drainage, repeated if necessary, may be sufficient provided that symptoms and signs of the disease are observed early and the treatment is introduced on time with the good response [15], as shown by the prospective randomized study conducted by Smith and associates [16]. If the condition does not improve, the next step is irrigation-suction drainage of the joint. It is necessary to make an open arthrotomy, remove the pus and wash out the joint profusely. In the case of osteoarthriti­sis, a possible bone sequestrum must be removed by arthro­tomy and curettage [12]. AHO and SA may result in permanent disabilities. An infection of the shoulder joint can cause disorders of growth of the humerus and the consequent forearm shortening as well as the occurrence of secondary ossification centres in proximal humerus and humeral head deformity [17,18]. This shortening and deformity of the shoulder bone may cause both functional (decreased range of motion in the shoulder joint) and aesthetic problems. Therefore, clinical and radiographic follow-up of these children during growth by paediatric orthopaedist is necessary.

Conclusion

Acute hematogenous osteomyelitis and septic arthritis are not common diseases, but represent a real diagnostic and therapeutic challenge, particularly in newborns. Timely diagnosis and prompt antibiotic and surgical therapy are prerequisites for healing without damage to the anatomy and function of the affected joint. That is why these diseases represent a real emergency implying a multidisciplinary approach, which should be taken into consideration by all specialists involved in the treatment of newborns.

References

Matić A, et al. Acute osteomyelitis and septic arthritis

Sažetak

Uvod
Akutni hematogeni osteomijelitis i septični artritis retka su oboljenja koja se često istovremeno javljaju u novorođenačkom uzrastu – oduđa zajednički naziv osteoartritis. Prikazana su dva prevremeno rođena novorođenčeta obolela od osteoartritisa ramene kosti i zgloba.

Prikaz slučaja


Zaključak
Rana dijagnoza osteoartritisa u novorođenačkom uzrastu nije laka jer se oboljenje retko javlja, a simptomi i znaci su oskudni i nespecifični. S druge strane, rano prepoznavanje i promptna i adekvatna terapija osteoartritisa od ključnog su značaja za povoljan ishod ovog oboljenja. Akutni osteomijelitis i septični artritis u novorođenačkom uzrastu dijagnostički su i terapijski izazovi.

Ključne reči: Osteomijelitis; Septični artritis; Osteoartritis; Zglob ramena; Humerus; Prevremeno rođeno dete; Dijagnoza; Infekcija + terapija

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