Diagnosis and treatment of aseptic femoral head necrosis

Jonibekov Jasur Jonibekovich State Medical Institute Bukhara, Uzbekistan

ABSTRACT

Aseptic femoral head necrosis is a multifactorial disease characterized by the occurrence of femoral head collapse with progressive development of severe secondary coxarthrosis. Clinically, the disease is manifested by progressive pain and limited range of motion, Trendelenburg's symptom, crepitation and instability of the femoral head. Treatment includes surgical interventions and correction of cytoactivity. There is evidence of the ability of bisphosphonates to prevent femoral head collapse.

Keywords: Aseptic femoral head necrosis, osteonecrosis, Leiden factor V, interleukin, cross-linked N-terminal telopeptide, tumor necrosis factor α.

Etiology and pathogenesis

Aseptic necrosis of the femoral head (ANGBC), avascular necrosis (International Classification of Diseases, 10th revision) is a multifactorial disease affecting mainly young people, leading to the development of secondary severe osteoarthritis of the hip joints with subsequent disability [32]. As an independent disease, it was first described by E. Bergman in 1927 and E. Freund in 1939. Initially, ANGBC was compared to Perthes disease in children, suggesting that adults use the same term, but in children, unlike adults, the disease often ends in recovery bone tissue with preservation of the femoral head. The disease usually develops at the age of 35-55 years (mean age 38 years). Data on the prevalence of the disease in the general population are not provided. However, it is noted that in the United States, between 10,000 and 50,000 new cases are diagnosed each year [4, 6, 32, 38]. Only 20% of individuals develop angioedema at the age of over 50 years [3]. The ratio of men to women is 3: 1, and half of the patients have a bilateral lesion. Approximately 5-18% of all hip replacement surgeries are performed concerning the primary ANGBC [3, 4, 16]. There are two types of pathological osteonecrotic process: medullary and ethmocortical involving the joint. Medullary osteonecrosis develops when the blood supply to the bone marrow canal is disrupted, resulting in the death of trabecular bone cells. Latticocortical osteonecrosis involving the joint has a more severe course (Figure 1). The risk of vascular disorders is usually noted in the proximal femur, both the trabecular and subchondral bones die, and this area is not able to calcify, as in medullary necrosis [19]. Aseptic necrosis of the femoral head occurs due to impaired blood flow and necrosis of the bone marrow elements of the femoral head. Among the main risk factors are long-term use of glucocorticosteroids(corticosteroids), autoimmune diseases, alcoholism, smoking, injuries and surgical interventions on the joint. There are also data on the influence of coagulopathies (thrombophilia and disseminated intravascular coagulation), pancreatitis, coagulation disorders, some autoimmune diseases, and systemic lupus erythematosus on the development of the disease, radiation, sickle cell anemia, hyperlipidemia, fat embolism syndrome, hip dysplasia, chemotherapy and/or radiation

therapy, organ transplantation, chronic liver diseases, and metabolic bone diseases. However, according to various authors, approximately 40-50% of cases of angioedema are described as idiopathic without etiological factors [2, 16, 35]. According to recent data, among the causes of idiopathic angioedema, great importance is attached to blood clotting disorders, in particular, thrombophilia in such patients occurs in several cases. times more often [10]. Some authors suggest that ANGBC is the result of genetic abnormalities. Another working hypothesis states that cell death occurs as a result of both an increase in intraosseous pressure of the femoral head, leading to a deterioration in blood supply, and a mechanism similar to the compartment syndrome [12]. According to recent data, approximately 40% of patients receiving corticosteroid therapy develop varying degrees of angioedema [45]. It should be noted that in addition to the fact that the use of corticosteroids is one of the etiological factors of angioedema, they stimulate apoptosis of osteocytes. It is assumed that corticosteroids disrupt the blood circulation of the femoral head, causing tissue ischemia. Bone marrow adipocyte hypertrophy is also induced, which increases intraosseous pressure [4]. In order to identify biomarkers of GCS-induced ANGBC, a comparative study of the expression of individual serum proteins in patients with osteonecrosis and in healthy volunteers was conducted. A significant decrease in the expression of C3-and C4-components of complement, inter-α-heavy trypsin inhibitor H4 and α2-macroglobulin was revealed in patients with osteonecrosis. These proteins are actively involved in these processes within vascular coagulation, apoptosis, and redox reactions [7]. In addition, since angioedema is a multifactorial disease, it is necessary to take into account predisposing factors for the development of GCS-induced osteonecrosis. In experimental studies on rats, L. Tian et al. The disease was associated with activation of osteoclasts via Toll-like receptor-4 (TLR4) signaling pathways [34]. The mouse genome is 90% similar to the human genome, which suggests similar pathogenetic characteristics of osteonecrosis [34]. According to recent data, TLR stimulation is involved in the pathogenesis of inflammatory and autoimmune diseases. When corticosteroids are used to treat these diseases, anti-inflammatory activity is realized through the suppression of nuclear factor kB (NF-kB), which, in turn, contributes to the development of angioedema. Effects on TLR7 or TLR9 and on interferon

It is suggested that impaired differentiation of mesenchymal cells may be a potential mechanism of angioedema pathogenesis. Arterial occlusion is considered the main predisposing factor; there are two main mechanisms: thrombosis and embolism. Arterial thrombosis can develop in two ways, acting synergistically: this is the primary damage to the artery wall and the primary pathology of coagulation. Some authors describe thrombosis caused by endothelial damage due to atherosclerosis or other diseases that cause vascular occlusion. In healthy people, the balance between thrombosis and thrombosis is controlled. in the presence of hereditary or acquired thrombophilia and / or hypofibrinolysis, this balance may change, leading to thrombosis. Another possible cause of angioedema is embolic disease. Impaired lipid metabolism leads to an increase in the amount of circulating lipids with reduced lipolytic activity of enzymes. Circulating lipids accumulate in the liver, contributing to fat degeneration and the formation of fat cysts. Rupture of cysts or spontaneous diffusion of fat droplets from the liver leads to fat embolism. The subchondral region of the femoral head represents This is the area of localization of fat emboli, both due to the small diameter and due to the location of terminal segments of arterial vessels in this zone. Intraosseous fat emboli cause stasis by mechanical occlusion, as well as damage to the endothelium by products of hydrolysis of free fatty acids. Another mechanism involved in pathogenesis is external capillary compression by hypertrophied bone marrow fat and cells with increased intracerebral pressure and circulatory disorders [19]. Blood supply to the femoral head is provided by the basicervical extracapsular valve. the articular vascular ring

and the ascending branch of the medial circumflex femoral artery, as well as small additional arterial tributaries of the lower and upper gluteal arteries of the round ligament [16]. In any case, the main cause of necrosis is acute ischemia caused by acute circulatory disorders of the femoral head (both arterial and venous). According to some researchers (Hungerford D., Leung P., 1983), the cause of these disorders is the peculiarity of blood supply to the femoral head in the form of a closed compartment (Fig. 2). Thus, the development of angioedema is described as a complication in femoral artery stenting [33].

In addition to the vascular factor, great importance is attached to the features of reparative bone regeneration in angioedema, which is disrupted in this disease. In the general scheme, the pathogenesis of this disorder can be presented as follows. Damage to the bone structure and violation of mechanical properties occur during the beginning of repair processes. For the formation of a new bone with effective mechanical properties, it takes 3 months, but for damage to the mechanical structure of the trabecular bone by osteoclasts, 3 weeks is enough. Thus, reparative processes become non-productive for the mechanical properties of the femoral head. Femoral head collapse occurs under mechanical stress (Fig. 3) [38]. Despite the fact that in the Russian-language literature the term “osteonecrosis”is used to denote the disease, emphasizing the aseptic nature of the pathology, in the English-language literature the term "osteonecrosis" is used. Moreover, the literature does not provide data that convincingly prove the absence of a role of bacterial or viral agents in the development of the disease. In the studies of R. F. Wideman, R. D. Prisby, a direct analogy of bacterial pathogenesis was made. osteomyelitic chondron necrosis of the femoral head in broiler chickens with aseptic necrosis in humans [43]. Bacterial chondron necrosis of chickens is initiated by microtrauma of chondrocytes of the proximal femur, followed by hematogenic colonization of opportunistic bacteria. Factors affecting bacterial proliferation include stress-induced immunosuppression and dexamethasone use – which increases the incidence of bacterial chondron necrosis in broilers [43]. It is interesting to note the peculiarity of the human hip joint. So, this area is affected in 40% of all cases of bone tuberculosis, which is a very high rate. Usually mycobacteria enter the joint by hematogenic route from the primary focus.

The radiological picture of tuberculosis, characterized by severe periarticular osteoporosis, localized around the circumference by foci of bone necrosis and narrowing of the articular fissure, resembles that of angioedema. In this regard, in tropical regions, tuberculosis coxitis is sometimes mistaken for progressive stages of aseptic necrosis [16].

Clinical signs and symptoms of angioedema are very diverse and depend on the stage of the disease. In the initial stages, there may be minor bouts of pain for no apparent reason, often with a normal range of motion; pain is noted with internal rotation of the hip. With the progression of the disease, discomfort can be replaced by sudden attacks of severe pain. Such attacks can signal the presence of a collapse or fracture of the femoral head, leading to the final stage of degenerative changes. Further development of the disease is typically determined by increasing mechanical symptoms, including reduced volume and painful movements, Trendelenburg's symptom, crepitation and instability of the femoral head [12].

Clinically, angioedema is characterized by symptoms similar to those of coxarthrosis: 1) pain in the groin area, passing along the front and side of the high with radiation to the knee joint. Pain increases with exertion, radiates to the lower back, does not pass at rest and at night; 2) restriction of movement in the affected joint, characterized by impaired self-service; 3) lameness on the affected leg when walking; 4) rapid development of hip muscle hypotrophy on the affected side; 5) shortening of the hip. According to the Association for the Study of Blood Supply to bone Tissue (Association Research Circulation Osseous), there are four stages of angioedema: • Stage I - there are no changes on the radiograph; • Stage II- demarcation sclerosis of the femoral

head without collapse • * Stage III-femoral head collapse: stage IIIA - collapse <3 mm; stage IIIB-collapse >3 mm; • stage IV-degenerative changes [16]. Fractures on the background of bone necrosis. Radiologically, the femoral head is homogeneously darkened, its height is reduced, there is no structural pattern, the surface of the head is sometimes in the form of compacted facets, the articular gap is expanded. According to magnetic resonance imaging data, a necrotic defect in the head is determined • * Stage III - "sequestration". The head is flattened and consists of separate structureless isolated fragments different shapes and sizes, the femoral neck shortens and thickens, the joint gap expands to a greater extent • * stage IV-repair. The spongy substance of the femoral head is restored. On the radiograph, sequester-like areas are not visible, the shadow of the head is outlined, rounded cyst-like clearings; * Stage V-secondary deforming osteoarthritis. The bone structure of the femoral head begins to be traced, its shape is significantly changed, and the congruence of the articular surfaces is disturbed.

Interestingly, according to the latest data, femoral head collapse occurs in a relatively short period of time – 5 months [13].

Diagnostics Laser Doppler flowmetry and microsensory intraosseous pressure transducers are used to study the femoral head blood circulation [25]. Histological examination of bone tissue samples taken during the operation of endoprosthetics of the affected joint is of great importance. Histological examination allows you to diagnose the disease, differentiate it with other pathologies and determine the pathogenetic pathways of the process. With the progression of osteonecrosis, the bone structure changes significantly. Osteoclast activity increases in the subchondral zone and necrosis zone, while osteoblast activity increases in the sclerosis zone (Figs. 5, 6) [39]. Immunohistochemical examination of bone samples revealed that the subchondral and necrotic zones were positive for the NF-kB receptor activator (RANK)

At higher magnification under a microscope, foci of newly formed bone tissue can be seen next to empty lacunae (Fig. In most cases, laboratory parameters, such as prothrombin time, activated partial thromboplastin time, are normal in angiotensin-angiotensin syndrome [16]. However, when comparing the parameters of patients with non-traumatic angioedema and healthy volunteers, significant deviations in the concentration of clotting factors in blood plasma were revealed. Thus, in patients with angioedema, a significant decrease in the level of ghrelin, an increase in the levels of von Willebrand factor, an inhibitor, was determined plasminogen activator-1(PAI-1), C-reactive protein in comparison with the control group, which indicates the involvement of these factors in the pathogenesis of the disease [20]. Determination of the level of interleukin-33 in blood plasma is proposed as a diagnostic marker of the development of angioedema. In a study conducted in 125 patients with angioedema, they showed a significant increase in interleukin-33 levels (174.33 pg/ml) compared to healthy individuals (90.5 pg/ml), regardless of the cause of osteonecrosis [48]. Complex biomarkers for the early diagnosis of angioedema are proposed: OPG, RANKL, cross-linked N-terminal telopeptide (NTX), C-terminal procollagen I peptide (PICP), tumor necrosis factor α, and interleukin-1β1 for enzyme-linked immunosorbent assay. Examination of patients with angioedema revealed statistically significant differences in this complex in comparison with healthy individuals [11]. Table 1 shows the diagnostic criteria for angioedema according to the literature data. It was found that the development of osteonecrosis is associated with a violation of osteogenic differentiation of mesenchymal stem cells [13]. This fact has been confirmed in both experimental and clinical studies by the effectiveness of drugs that correct the differentiation of these cells, as well as the effectiveness of stem cell therapy. Genetic studies can not only confirm the validity of disease therapy, but also serve as a way to find new, more effective methods for early diagnosis and preventive treatment of osteonecrosis. In this regard, the study of associations of genetic markers with ANGBC is a promising method.

Treatment

Aseptic necrosis of the femoral head is a progressive disease that quickly leads to hip joint dysfunction and disability of the patient, so the development of effective methods for treating this pathology is an urgent problem in modern orthopedics. Since the pathogenesis of the disease involves two main mechanisms – vascular (circulatory disorders) and tissue (pathology of osteocytes, osteoblasts and osteoclasts), treatment methods are aimed at these links. At the initial stages of osteonecrosis, organ-preserving procedures are performed, including both surgical treatment and and the use of various medications and stem cells [38]. Aseptic necrosis most often develops in young and middle-aged people. Since total hip replacement does not always provide optimal results for these patients, various procedures are performed to preserve the joint in the early stages of the disease: central decompression, percutaneous drilling, vascular and non-vascular bone grafting, and rotational osteotomy. However, the assessment of the success of these operations is very variable [19]. Initial treatment in the early stages ANGBC consists of unloading therapy, which is necessary to prevent damage to the blood vessels supplying the femoral head and its subsequent collapse. However, this tactic only leads to positive results in 20% of cases. In 80% of cases and more, it is necessary to resort to surgical interventions, including total hip replacement (arthroplasty) and other techniques. Among the surgical techniques used is transversal rotational hip osteotomy, which has been used since 1972 (Figs. 9, 10). However, in 40% of cases there are complications in the form of instability of the femoral head [38]. The essence of the operation is to move the necrotic area of the femoral head to the area that is subjected to the least mechanical stress. The ideal surgical strategy for angioedema is to remove necrotic bone tissue from the femoral head, replace it with a viable and strong bone, then restore the viability of the head and prevent the collapse of the articular surface. For this purpose, non-vascular and vascular bone transplantation is used. The vascular-free technique is used in the state of pre-collapse and minimal post-collapse with relatively preserved articular cartilage. In the postoperative period, 85% of patients manage to get rid of symptoms with minimal progression of osteoarthritis. As a graft, the patient's own fibula is mainly used [38]. Vascularized bone transplantation provides prognostically better results and allows the restoration of the subchondral surface at later stages of the disease. For transplantation, for example, a vascularized section of the fibula is used. Statistically significant results They were obtained during bone transplantation on a triple muscular stalk using the sartorial muscle, the femoral broad fascia muscle, and part of the gluteus medius muscle (36 patients, postoperative follow-up for 10-24 weeks) [28]. Joint-preserving techniques, such as internal decompression, vascular or vascularized bone grafting, and various types of hip osteotomy, are most promising in the early stages of angioedema while preserving the structural relationships of the subchondral layer. In addition, a promising direction is to enhance bone regeneration, transplant osteogenic cells, etc. or angiogenic progenitor cells in combination with auxiliary growth factors. In this area, multipotent mesenchymal stem cells isolated from an adult are the most promising candidates among various cell types [32, 37]. A model of transplantation of mesenchymal stem cells transgenic by the growth factor of hepatocytes was developed in the experiment [42]. Axial decompression is a widespread procedure in the treatment of angioedema in young patients. The effect of this operation is realized by reducing intraosseous pressure (Fig. 11). However, axial decompression in osteonecrosis only eliminates the clinical symptoms and has almost no effect on the progression of the disease [21]. Experiments on rabbits have proven the best therapeutic effect of creating negative pressure in the tissues of the femoral head in osteonecrosis in comparison with axial decompression. The effect is associated with the stimulation of vascular proliferation, increased blood circulation and osteogenic differentiation of bone marrow stromal cells. A higher expression of vascular endothelial growth

factor (VEGF) and BMP2 was detected when using a negative pressure in comparison with internal decompression [46]. The method of axial decompression with replacement of bone tissue with synthetic materials (calcium sulfate and calcium phosphate) turned out to be more effective [44]. According to a meta-analysis, bone marrow mesenchymal stem cell transplantation demonstrated better therapeutic efficacy compared to axial decompression [21]. Based on Q's data. Mao et al., by injecting native bone marrow mononuclear cells (100-200 ml) enriched with mesenchymal stem cells (30-60 ml) into the medial circumflex artery of the femur followed by [26]. Combined techniques, such as mesenchymal stromal cell transplantation supplemented with vascularized bone grafting, have proved to be the most promising and effective [1]. Less successful were such techniques as a combination of axial decompression with injections of own bone marrow taken from the iliac crest [8]. However, in most cases, it is not possible to prevent the progression of the disease and the main method of treatment remains total hip replacement, especially in the late stages of osteonecrosis with collapse 13, 14) [16]. The prognosis of life expectancy after endoprosthetics depends on the possible development of complications such as edema of the femoral bone marrow. In this regard, it is necessary to strictly follow the technique of surgical treatment and postoperative management of patients [23]. Hyperbaric oxygenation is also used for the treatment of angioedema, with long-term use of which positive results were noted both in terms of regression of clinical symptoms and according to magnetic resonance imaging data. Recent clinical studies have shown that bisphosphonates they enhance osteoclast apoptosis and prevent femoral head collapse [24, 38]. In addition to the methods used in clinical practice, it is necessary to focus on promising experimental methods, which is associated with unsatisfactory results of many organ-preserving methods currently used. In the development of the most reasonable methods of treatment, genetic research methods are of great help in order to identify risk factors for osteonecrosis as a target for therapeutic action. In recent years, many articles have been published about 12. X-ray picture of stem cell insertion into the medial circumflex artery of the femur (arrow) [26]. (a) (b) Figure 13. Total hip replacement. 14. X-ray picture of ANGBC before (a) and after (b) total hip replacement. The latter is a key factor in bone remodeling, controls the processes of angiogenesis, and is used as a therapeutic agent to enhance neovascularization. When using VEGF in the experiment, successful results were obtained in preventing angioedema by stimulating angiogenesis and enhancing repair [38]. Noteworthy is the work of H. Zheng et al., which showed a significant decrease in the incidence of GCS-induced angioedema when using gastrodin – one of the components of the herb Gastrodia elata Bl, which has an anti-apoptotic effect [47]. The data obtained indicate not only the possible prospects for drug treatment of osteonecrosis, but also the features of the pathogenesis of the disease, in which enhanced apoptosis of osteocytes plays a key role [24]. Statistically significant enhanced osteocyte apoptosis and osteoblasts, regardless of the etiological factor, was identified in the work of E. Mutijima et al. The studies were conducted on histological material of patients who underwent total joint replacement. Enhanced apoptosis was observed in the area of necrosis [29]. Among TLR antagonists, TAK-242 is used to treat autoimmune and inflammatory diseases. Since the role of TLR in the pathogenesis of GCS-induced angioedema has been proven, this substance may become the drug of choice for its treatment [34]. In experiments on rats, the effectiveness of coenzyme Q10 for preventing the development of Corticosteroid-induced angioedema: in the main group, the disease developed in 20% of patients versus 70% in the control group [18]. Since it is known that among the etiological factors of angioedema, a certain role is played by the pathology of the blood coagulation system (a significant decrease in ghrelin levels, an increase in the levels of von Willebrand factor, PAI-1, and C-reactive protein), anticoagulants are supposed to be used in the treatment of this disease [20]. For

example, in the studies of R. Beckmann et al. In experiments on rabbits, enoxaparin was shown to be effective in preventing GCS-induced osteonecrosis. In clinical trials in the treatment of patients with angina pectoris, enoxaparin prevented the progression of the disease at stages I-II [4].

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