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The physiopathology of avascular necrosis of the femoral head: an update

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ABSTRACT

The physiopathology of the femoral head bone necrosis is similar for children and for adults. The disease is characterized by apoptosis of bone cells – bone marrow and bone forming cells-resulting in head collapse with a subsequent lesion of the overlying cartilage, and therefore flattening of the rounded surface shape of the head articulating with the acetabulum, provoking, eventually, secondary osteoarthritis. When the disease becomes clinically evident already destructive phenomena have occurred and collapse will eventually ensue. In children, because epiphyseal cartilage has growth capabilities, lost epiphyseal height can be recovered, however in adults collapse is irreversible. In this paper the physiopathology of this disease is examined as well as its implication for treatment. Prevention by genetic studies is discussed.

Introduction

Avascular necrosis of the femoral head (ANFH) is not an uncommon disease characterized by apoptosis of bone cells – bone marrow, bone forming, and bone destroying cells-resulting in bone collapse with a subsequent involvement of the overlying cartilage, provoking flattening of the head surface with, eventually, development of secondary osteoarthritis [1–10]. In children, since most of the head cartilage has growth properties – the so called epiphyseal cartilage-restoration of head height and shape is possible and arthritis avoidance may be a fact. The younger the child is the greater the capacity of growth and, consequently the regeneration potential [11–14].

The denomination "avascular" is very peculiar as the femoral head blood supplying vessels do not disappear; rather they suffer a pathological process which results in blood flow interruption.

Although the nature of ANFH is basically defined upon the death of cells, in the adult as well as in children, the diagnosis is normally made by images obtained through a non-invasive method, either with x-rays or magnetic resonance (MRI). Therefore, what usually characterizes the disease is the augmentation of bone density under x-rays, with a subsequent disturbance of the femoral head shape in a limping patient with groin, thigh or even knee pain. Since the disease is usually silent for an undetermined time, former physiopathological events are ignored by the time the clinician receives the patient.

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Aetiology of the ANFH

Bone necrosis can be grouped according to its etiology in traumatic and non-traumatic cases, and also within these two groups, as pediatric or adult.

Many diseases, medicaments, and conditions are classified under non-traumatic cases, as a complication of the original disease.

Traumatic cases are usually the result of a femoral neck fracture, and although the most common denomination for atraumatic ANFH has been idiopathic, a metabolic disorder background is the most common keystone in every patient. The hepatic metabolism is usually altered either by a primary syndrome, by alcohol intake or by the administration of steroid medication for an immunogenic or autoimmune disease.

Alcohol is the most common etiology in adults; its intake is dose-dependent being demonstrated that the relative risk of the disease is 3.3 if the intake is over 400 ml per week, 9.8 if the intake increases to 1 liter and up to 17.9 if more than this amount per week is consumed [15]. What alcohol disturbs is phospholipid and cytokines metabolism [16] but the final mechanism of how the blood supply interrupts and the bone cells of the femoral head die is unknown [17]. That is why patients developing antiphospholipid antibodies have threefold higher risk of presenting an ANFH than control population as well as some other metabolic diseases such as Gaucher's disease [18].

Other disorders such as sickle cell hemoglobinopathies, mainly homozygous sickle cell disease, present bone necrosis as a complication. It has been estimated that after 35 years of the disease onset, 50% of the patients have developed bone necrosis [19]. Haematopoietic cell transplantation also can provoke bone necrosis which might be based

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on a similar mechanism as hemoglobinopathies [20]. Some other blood diseases such as inherited thrombophilia and hypofibrinolysis have also been related with the onset of bone necrosis with a gene mutation mechanism suggested [21–29].

Steroid administration and diseases treated with steroids are also one of the main etiologies of ANFH. Similarly to alcohol, steroids are also dose-dependent in their role of etiology agent of femoral head bone necrosis. Higher doses than 20–40 mg per day, mainly in prolonged treatments, have more chance of developing the disease [30].

Autoimmune disease such as Systemic Lupus Erythematosus (SLE) can be associated with ANFH [31]. Its association with glucocorticoids administration further increases the risk of the necrosis provoked by vasculitis; duration and doses of treatment influence the proclivity of developing bone necrosis [32–34]. Those patients having associated conditions because of SLE disease develop more bone necrosis than the rest [32–34].

Other diseases that have been related to bone necrosis include Human Immunodeficiency Virus (HIV) infection [35,36] via fat testosterone mechanism but apparently not related to antiretroviral therapy [36], radiation, heritable COL2A1, or bisphosphonate use. A thorough updated review of diseases and conditions provoking ANFH can be found elsewhere [19,37].

Although what has been described above is known to have the hazard of provoking ANFH the intimate mechanism of how the vascular flow ceases remains obscure. Microangeitis can easily provoke thrombosis and ensuing necrosis but that has not been proven in the role of the disease. Therefore, the denomination of idiopathic or essential for the phenomena triggering the bone necrosis and its physiopathology is appropriate. We just know associations but not etiological events correlation with physiopathology.

Children can also have necrosis of the femoral head bone epiphysis, and, as the adults, the disease can be either traumatic or not. Many diseases have also been described to provoke bone necrosis in the child but they are mainly metabolic in origin. Cultural, geographical and genetic circumstances have also been related with idiopathic cases, the so-called Legg Calvé Perthes' Disease (LCPD). Studies from the eighties onwards have elucidated many situations related with this disease but nothing is clear so far in relation to its etipathogenesis.

Physiopathology of ANFH

Bone necrosis physiopathology is very similar in children and adults. What differentiates both age groups is cartilage maturity. Since children have epiphyseal growth cartilage capable of repairing femoral head height, loss occurred during disease evolution can be restored; however, matured patients cannot compensate that because the thin epiphyseal cartilage is just articular and has not growth aptitudes. Growth potential is so important. The younger the child is the better the prognosis will be [13,14].

The sequence of events occurring in the physiopathology of bone necrosis in adults as well as in children has been constructed by interacting knowledge from animal experimentation with human clinical and images observations, and bone biopsies. Therefore, conclusions about whether events here described are for sure or not, is not yet supported by very strong arguments. According to them, bone necrosis evolution can be divided into two successive phases: ischemia and regeneration [3,7,8,10,38].

Ischemia phase

The timing as to when ischemia starts is very difficult to know, since once the disease clinically onsets, it has usually been silent for long. Also the background, in adults and in children, is unknown in many cases. This is applicable for non-traumatic cases and also in traumatic ones as although a fracture is the origin of ANFH, why in many instances worse fracture patterns do not end in an ANFH whereas some more benign cases develop the disease remains unknown.

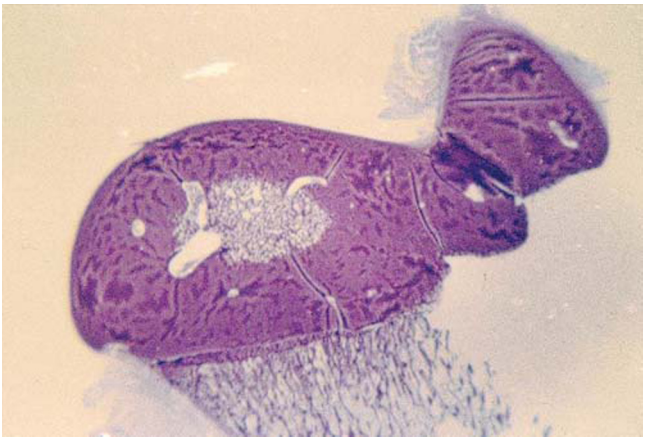

Fig. 1. Femoral head of a 5 week old rabbit. The bony epiphysis can be seen surrounded by the epiphyseal cartilage which is pierced by canals for vascular supply to the bone.

In non-traumatic pediatric cases the theories on its etiopathogenesis were developed between the fifties to the nineties, and still it is not clear if the origin of the ischemia is in the vessels nourishing the epiphysis [39–44], in the blood they transport [45] or in the cartilaginous matrix surrounding the cartilage piercing vessels [46–50]; this last hypothesis is mainly supported by pathological findings [51–53], and also by studies on either prenatal [54–57] or postnatal periods [58–61].

According to this constitutional theory, the altered growth cartilage composition would facilitate breakdown of the blood supplier canals to the bony epiphysis [38,62,63] (Figures 1 and 2). Then as the blood flow to the head is interrupted with subsequent ischemia of the bony epiphysis, it would be expected that child complains of pain. Yet, we know that either pediatric or adults cases do not come to the doctor in this early situation, rather they do when the regeneration phase is well in progress. Since long, studies on transient synovitis of pediatric hips in non-traumatic cases, -characterized by hip pain of unknown origin during a short period- have failed in relating this disease with early onset of LCPD [44]. Hence, it can be thought that bone ischemia does not always provoke pain, at least in early phases. The same comes true for adults.

For image-pathology correlation, the majority of imaginings studies on this early ischemia phase mainly come from animal

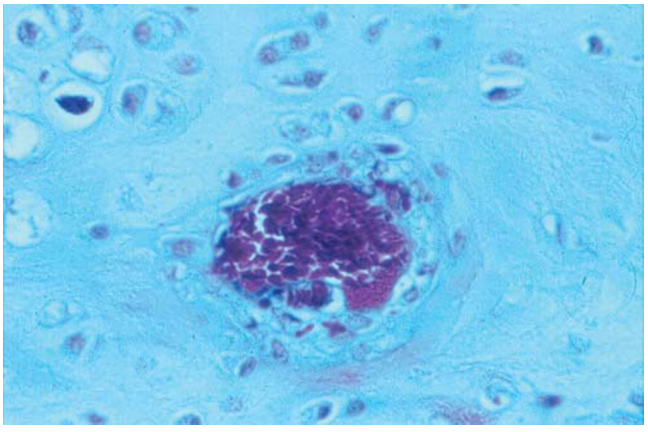

Fig. 2. Femoral head of an 11 week old rabbit treated with oxytetracyline. A vascular tunnel piercing through the epiphyseal cartilage of the femoral head can be seen. Blood flows through it.