REVIEW ARTICLE

Acquired chondronecrosis

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Abstract

Zonal necrosis of chondrocytes is a characteristic feature of Kashin-Beck disease. Inferences about chondronecrosis in several spontaneous and experimental arthropathies of other species may be relevant to the cause of Kashin-Beck disease and conceivably, too, banal osteoarthritis in man.

Although it is not commonly recognised as a category of the general disease of joints, selective necrosis of articular and growth plate cartilages occurs with a distinct prevalence in humans and several animal species. In man the prototype is Kashin-Beck disease. Chondronecrosis in other human disorders occurs in more complex circumstances. 'Laminar chondritis' or, as it is now known, idiopathic chondrolysis, was originally described as a necrosis of articular cartilage in young children. Cell death is, however, not the definitive event.¹ Necrosis of cartilages is a feature of inherited adenosine deaminase deficiency. Affected infants die long before locomotor disabilities are manifest.² Death of chondrocytes is also the rule in ochronotic cartilage.

The animal lesions, spontaneous and experimental, have no defined human analogues. Nevertheless, they share several important features with Kashin-Beck disease: they are acquired and affect growing individuals; damage or necrosis of articular chondrocytes leads to osteochondritis dissecans and osteoarthritis; and involvement of growth plate cartilage results in disproportionate dwarfism and malformation of the skeleton. These features suggest that at some early stage in the life of skeletal chondrocytes the cells are particularly susceptible to defined noxious agents or else have special metabolic requirements.

This article reviews the comparative pathology of the several disorders and the environmental factors that may be involved in their cause. Although chondrocytes are the apparent seat of the disease process, the possibility that the primary disturbance resides in the subchondral microcirculatory bed, and that the viability of the cells is compromised as a consequence, cannot be dismissed out of hand; nor can the possibility that primary changes in the pericellular matrix embarrass the nutrition of the cells.

Kashin-Beck disease

This non-inflammatory joint disease is widely

prevalent in parts of northern China and neighbouring Siberia.³ Perhaps two million people are affected, many of them terribly crippled. In some communities the prevalence is up to 85% of the population. All evidence indicates that Kashin-Beck disease is of environmental origin. The earliest morphological change is coagulation necrosis of the deepest zone of the articular and epiphyseal growth plate cartilages of preadolescent children. Detachment of articular cartilage gives rise to loose bodies later on as well as deformities of multiple appendicular joints. Stunting of growth at times is marked.

Despite intensive studies by Russian, Japanese, and Chinese investigators over the course of the last century no toxic material has been identified as responsible for Kashin-Beck disease; nor has a specially required nutritional factor for the cartilages been found. There is no evidence for an infectious agent. Three types of thinking are now entertained in different research laboratories: (a) trace metal toxicities, perhaps complicating excessive phosphate ingestion; (b) mycotoxicosis arising from grains contaminated by *Fusarium oxysporum*; and (c) deficiency of selenium. The incidence of Kashin-Beck disease in Siberia has declined as food has been brought in from other areas. Selenium deficiency may be responsible for the cardiomyopathy, Keshan disease, that also is endemic in that part of the world, but its link with Kashin-Beck disease is at best tenuous.

Osteochondrosis

This term applies to one or more veterinary disorders of great economic importance to the livestock, kennel, and poultry industries. There are many reports on the subject, few of which are known to the medical profession. Like Kashin-Beck disease, osteochondrosis occurs in very young animals and has as its principal target the joint and growth plate cartilages. Lameness, osteochondritis dissecans, stunted growth, and, ultimately, osteoarthritis are characteristic of cases with advanced disease. There are variations from species to species, and we may be dealing with more than one entity.

Focal failure of endochondral ossification and hence persistence of nubs of basilar cartilage is a prominent feature of osteochondrosis in swine and dogs. This is often associated with necrosis and horizontal splitting of articular cartilage at the junction of the hypertrophic and calcified layers.⁴⁻⁶ The necrosis at times is sufficiently extensive for it to resemble Kashin-Beck disease.

The cartilage in these regions often splits off and becomes a loose body. If the animal lives past early marketable age the lesion progresses to osteoarthritis. The illustrations in a recent paper published by the *Annals* reporting experimental production of Kashin-Beck disease suggest that rhesus monkeys also are susceptible to osteochondrosis.⁷

Epiphysiolysis is another common feature of swine osteochondrosis, which may occur in the absence of changes in the joint cartilage. The question has been raised as to whether these may be two separate entities that sometimes coincide in the same animal. Osteochondroses are generalised processes but their expression is not uniform in all joints. Variation in the distribution may be due to differences in mechanical loading of the particular cartilage or to anatomical peculiarities of individual epiphyses.⁵

There are species differences in the character of osteochondrotic lesions. In young horses destructive changes dominate and there is little unresorbed basilar articular cartilage.⁸ Some evidence suggests that different mammalian species have varying susceptibilities to trace element toxicity.⁹ The size of animals also affects viability of articular chondrocytes. In small laboratory rodents¹⁰ and in pigeons segmental necrosis of chondrocytes occurs with aging. It is in these sites that osteoarthritis supervenes. When it does, the devitalised segment is prone to slough off as a unit rather than to be fibrillated as in man.

Abnormalities of trace elements have been invoked in osteochondrosis of ruminants and other livestock. Abnormally low copper concentrations may be a prime factor in foals.⁸ One suggestion is that cartilage collagen becomes abnormal in copper deficiency because lysyl hydroxylase is a copper dependent enzyme. The same end result may be brought about by poisoning with trace metals—molybdenum, zinc, or cadmium—that displace copper from the sulphhydryl binding sites of intestinal metallothioneine.⁹ The skeletal abnormalities have been found in field animals close to smelters. Children in the same areas have no clinical abnormality. Their diet is more varied than that of the equines, of course, and they do not ingest the same quantities of these trace elements.

Angiographic studies have disclosed poor perfusion of minute subchondral vessels near to osteochondrotic foci in swine.⁴⁻⁶ Inasmuch as chondrocytes are the source of antiangiogenesis factor we do not yet know whether the micro-circulatory changes are the cause or the result of the cell damage.

The cardinal feature of avian osteochondrosis, tibial dyschondroplasia, is failure of the provisional metaphyseal cartilage to become calcified in preparation for replacement by bone.¹² Unlike the mammalian counterpart, necrosis of chondrocytes is not seen. Tibial dyschondroplasia has several causes,¹³ but of particular interest for present purposes is a water soluble product of *Fusarium roseum granulearum*, fusarochromanone. Ingestion of this toxin or large amounts of the mould by baby chicks rapidly results in tibial dyschondroplasia.¹² Fusarochromanone

has little cytotoxic effect on rabbit articular chondrocytes in monolayer culture.¹⁴ There are, as yet, no reports on cultured chick chondrocytes, but the observations do not indicate that this toxin is significant in Kashin-Beck disease. The possibility that the action of this mycotoxin is exerted specifically against mineralisation of the particular cartilage has not been tested.

Experimental chondronecrosis

Antibacterial quinoline compounds cause lameness associated with cystic necrosis of articular cartilage in young puppies¹⁵; mature dogs are resistant. The lesions are self limited and repair through proliferation of neighbouring chondrocytes when the drugs are withdrawn. Until recently only canines were considered susceptible. Kato and Onodera, however, have reported similar changes in rats given ofloxacin.¹⁶ Rare clinical reports of human arthritis following treatment with this type of drug are difficult to interpret for chondronecrosis.¹⁷

There is some information, too, about deficiency of trace elements in relation to cartilage. Vanadium is an essential element, even though its precise function is not known. Sulphated glycosaminoglycan synthesis by rabbit chondrocytes in culture was enhanced by low concentrations of vanadate (6 µmol/l) but inhibited by higher doses (40–60 µmol/l).¹⁸ Kids, born of vanadium deficient goats, had painful and deformed acral joints, but the state of the cartilage was not described.¹⁹ Comparable experimental deficiencies of nickel, selenium, lithium, or fluorine did not cause similar abnormalities.

Thallium produces chondrocyte damage in the growth plate of chick embryos.^{20, 21} That observation is relevant to this inquiry for two reasons: (a) there is a selectivity for one population of chondrocytes—those of the hypertrophic zone; (b) there is a window of time in which the susceptibility to the toxicity is maximal: the 11th day of incubation.

Concluding remarks

Aside from the arthropathic consequences of overt chondronecrosis, several considerations invite speculation as to whether lesser degrees of acquired chondrocytic damage contribute to banal degenerative joint disease. Two observations suggest that this may be so. Firstly, the distribution of spontaneous osteoarthritis in elderly dogs corresponds to the distribution of osteochondrosis in puppies 3 to 9 months old.²² Secondly, some years ago a highly experienced Soviet investigator noted that adults moving into areas in which Kashin-Beck disease was endemic were particularly prone to develop primary osteoarthritis.²³ This was an anecdotal statement and no supporting data were presented. The idea commends itself to systematic testing by epidemiologists interested in rheumatic disease. Perhaps, too, possible cartilage damaging effects of non-steroidal anti-inflammatory drugs²⁴ and chemotherapeutic²⁵ agents should be examined in like vein.

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