Radiographic findings in hereditary multiple exostoses and a new theory of the pathogenesis of exostoses

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Abstract. Analysis of 330 exostoses in 18 patients affected by hereditary multiple exostoses disease suggested a new classification of exostoses as eccentric or full-thickness. Radiographically arrest of metaphyseal remodeling with failure of coning and persistence of the primary metaphyseal trabeculae was evident in full-thickness exostoses. Similar bone lesions can be obtained experimentally with inhibitors of bone turn-over. A localized, peripheral defect in remodeling over a limited time can give a satisfactory explanation also for the origin of eccentric exostoses. The thesis that this is the basic mechanism of exostosis formation is presented.

Fig. 1. Distribution of age and localization of exostoses in the studied patients

Fig. 2. R. L., 10-years old. Eccentric exostosis of the distal tibia with remodeling of the fibula around exostosis
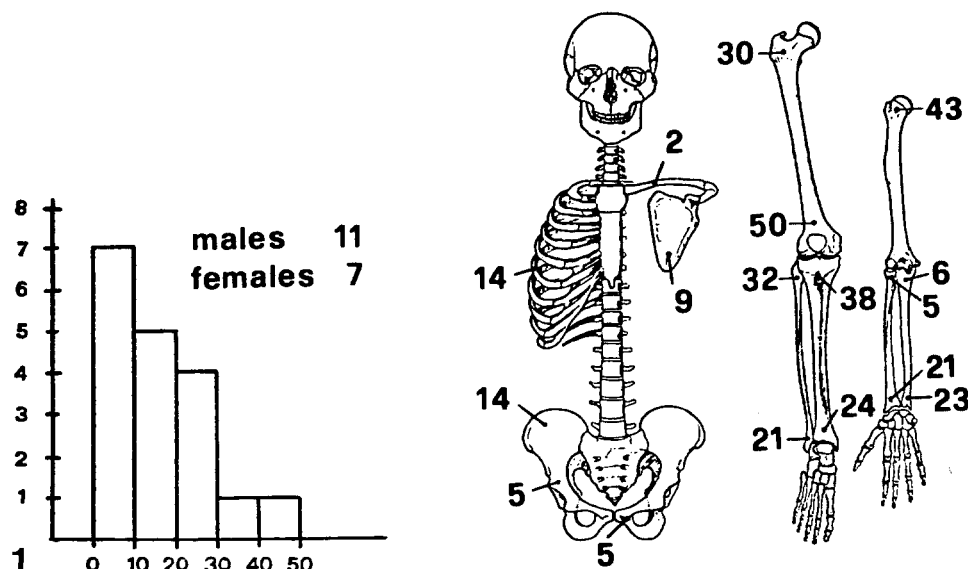
Multiple exostoses (HME) is a well known hereditary disease characterized by great variability in the number of exostoses, which is often very large, as well as in their shape, size and effects on bone growth. Exostoses also occur as solitary lesions which are not familial; they are usually classified as sessile or peduncolated according to the extension of their implant (type of attachment). The presence in a single patient with HME of pedunculated and sessile eccentric exostoses and the club-shaped thickening of the metaphyses suggest a common underlying defect, the nature of which cannot be explained by previous pathogenetic theories.

John Hunter first described multiple exostoses in his lectures on the Principles of Surgery delivered in 1786/87 and noted that as in rickets bone ends were enlarged; this led him to suppose that the two conditions were related [4].

A century later Virchow [15] suggested separation and rotation of a portion of the epiphyseal cartilage as the
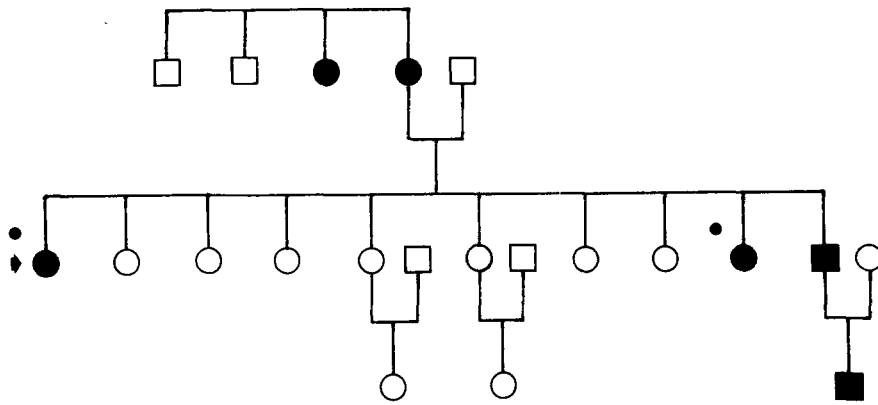
Fig. 3. F. P. A., 12-years-old, 6 family members with HME. Antero-posterior and lateral views of the forearm showing a full-thickness exostosis of the distal, radial metaphysis. The arrows indicate the line of arrest of metaphyseal remodeling. The cylindrical metaphysis is composed of thin trabeculae with a prevailing longitudinal pattern. A full-thickness exostoses of the ulna is also evident. Shortening of both the ulna and radius is present

pathogenetic mechanism of exostosis. In 1914 Müller postulated a theory based on the observation of chondrogenic cells in the periosteal layer [8] and shortly afterwards, in 1920, Keith drew attention to the mechanism of metaphyseal remodeling and the related anatomical structures and postulated a defect of the perichondral ring, a structure which is necessary to limit the growth of cartilage and prevent undue transverse growth [5].

In the present study interpretation of the radiographic features of 330 exostoses in HME leads us to propose a new classification and new pathogenetic theory of exostoses. As solitary and multiple lesions are histologically similar, it seems reasonable to assume that this theory is applicable to all exostoses.

Materials and methods

A skeletal survey was obtained in 18 patients from 13 families with HME seen in the Orthopedic Department of the University of Pavia. Eleven patients were seen for the first time in childhood before achieving skeletal maturity and seven were adult relatives. The age distribution of the subjects and localization of the exostoses are shown in Fig. 1.

Radiographic findings

A total of 330 exostoses was found in these patients and the number of exostoses per patient ranged from 4 to 28 with a mean of 18 per patient. The shape and volume of the exostoses was very variable and their appearance was often quite bizarre. Analysis of their radiographic appearance suggested a new classification as eccentric or full-thickness.

Eccentric exostoses have lost their connection with the adjacent growth cartilage; they probably migrate from the metaphysis as bone grows and in older patients can reach the diaphysis. Similar features are seen in solitary exostoses. Eccentric exostoses do not interfere with growth in length of the bone from which they arise. In the forearm or leg remodeling may occur in the bone adjacent to the growing mass (Fig. 2), or compression of the adjacent cartilage by the exostosis may cause a growth defect with tilting of the epiphyseal plate.

Full-thickness exostoses involve the entire circumference of the metaphysis. They are frequent in HME but have never been reported in solitary exostoses. The metaphysis is cylindrical with a line of arrest of metaphyseal remodeling clearly evident on the X-rays (Fig. 3). The trabecular pattern of the metaphysis is composed of thin longitudinal trabeculae which represent the calcified intercolumnar septa of the growth plate cartilage and primary metaphyseal trabeculae which have not undergone remodeling. Cartilage growth potential is severely compromised and results in shortening of the bone. As usually occurs with eccentric exostoses, growth recovery

Fig. 4. S. A., 6-years old. Recovery of growth and remodeling of a full-thickness exostosis of the ulna. The arrows indicate the line of arrest of metaphyseal remodeling. There has been some reorganization of the enlarged area and the longitudinal trabecular pattern is no longer evident

Fig. 5. O. G., 18-years old. Coxa valga in a full-thickness exostosis involving the upper femur. The *arrow* indicates the line of arrest of metaphyseal remodeling. The arched trabecular systems of the neck are replaced by longitudinal trabeculae

and remodeling was observed in one case of HME in this series (Fig. 4).

Others deformities characteristic of HME such as coxa valga (Fig. 5), bending of the radius, displacement of the radial head, epiphyseal tilting in varus or valgus can be explained by different growth rates of the bones in biosseous limb segments (forearm and leg) [1, 12].

Discussion

Of fundamental importance to admission in the present study is the prerequisite of a family history of HME, a criterion which should assure exclusion of all cases of endochondromatosis, a disease which is not transmitted genetically. Indeed, most older case reports of HME include examples of multiple endochondromatosis or Ollier's disease [13]; although a relationship between the two conditions was postulated in 1925 by Stocks and Barrington [14] it has since been established that they are separate entities. The criteria currently used for classifying exostoses are difficult to apply to the bizarre and complex features of full-thickness exostoses probably due to the fact that such criteria are based mainly on description of solitary exostoses or eccentric exostoses in HME. It is in fact difficult to postulate a theory of the

origin of exostoses which can explain the relationship between sessile and pedunculated exostoses showing eccentric growth and full-thickness exostoses not showing eccentric growth but maintaining the same width as the epiphysis. Hunter's suggestion that rickets and exostoses are related is in part true. Indeed the two conditions have in common an arrest of remodeling but differ in as much as calcification is inhibited in rickets but not in HME. Virchow's theory is supported by the recent experimental production of exostoses after transplantation of epiphyseal line cells under the periosteum [2] but does not give a satisfactory explanation of the arrest of metaphyseal remodeling in full-thickness exostoses, a defect also shared by Mueller's theory [8]. The theory of a defective perichondral ring as suggested by Keith supposes a lack of coordination between endochondral ossification, longitudinal growth and perichondral ring formation [5]. According to this theory it is held that growth plate cartilage increases its transverse diameter by apposition from the overlying perichondrium [3, 9].

Langeskjold on the contrary produced evidence that the epiphyseal cartilage expands peripherally by interstitial growth and that the outer layers of cartilage cells are transformed into the proliferative layer of the periosteum [6]. The origin of exostoses is consequently referred to the persistent chondrogenic properties of these cells in the periosteum.

Eccentric exostoses have a histologic appearance similar to that of the bone from which they arise with an outer layer of cortical bone and an inner marrow cavity; the cartilage cap repeats the columnar arrangement of the epiphyseal plate with all the phases of endochondral ossification. Unfortunately, the histology of full-thickness exostoses is unknown; however, radiographically arrest of metaphyseal remodeling with failure of coning and persistence of the primary metaphyseal trabeculae is evident even in the absence of histologic documentation. These
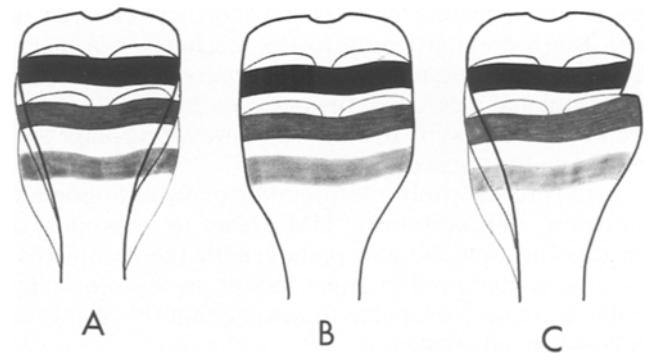

Fig. 6 A–C. Diagrams illustrating the effects of an inhibitor of osteoclastic resorption (EHDP) on the shape of tibial metaphysis in the rat (modified from Schenk et al. 1973): **A** the conical shape of the metaphysis results from resorption of the external metaphyseal trabeculae; the outline of the proximal tibia is superimposed at three subsequent times *(black line, dark grey line, gray line);* **B** complete inhibition of metaphyseal remodeling produces a cylindrically shaped metaphysis; **C** effects of a transitory, localized arrest of metaphyseal remodeling; growth potential of the exostosis results from the detachment and subsequent rotation of the fragment of growth plate cartilage

features can be observed in all such exostoses and in our opinion represent the basic mechanism of exostoses formation. A similar appearance can be obtained experimentally with inhibitors of bone turn-over such as diphosphonates, the main difference being that the latter also inhibit the calcification process [11]. In the same experimental model reduction in longitudinal growth of bones has been observed [10]; this finding fits with the shortening of bones observed with full-thickness exostoses and suggests the presence of a mechanism regulating resorption at the bottom of the growth plate and rate of cell proliferation at the top. An arrest of remodeling satisfactorily explains all the features observed in exostoses involving the entire metaphyseal area.

With regard to eccentric exostoses, according to this hypothesis, a localized peripheral defect in remodeling over a limited time gives rise to an eccentric piece of growth cartilage which with growth loses its connection with the original epiphyseal plate. This situation is represented in the figure illustrating the effect of inhibition of osteoclastic resorption in Shenk's experimental model [11] (Fig. 6). The most difficult problem with this model is satisfactory explanation of the rotation and eccentric growth of eccentric exostoses, since the linear arrangement of cartilage cells is no longer parallel to that of the original growth plate. However, if arrest of remodeling is transitory and perichondral resorption recommences, as demonstrated by the conical shape of the metaphysis in eccentric exostoses, the detached portion of cartilage will no longer be restrained by Ranvier's perichondral ring and in this situation tilting is easily foreseeable due to progression of the resorption/apposition process at the base [13] and to the growth potential of the unrestrained cartilage cap at the dome of the exostosis. An interaction between exostosis and periosteum can also explain the slower migration rate as compared to that of the original growth plate [7] as well as the rotation of the cartilage cap.

Most bone pathology textbooks include exostoses and HME in the sections on tumors but our theory of their pathogenesis suggests that they should be better considered among the genetic chondrodysplasias.

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