Hereditary Multiple Exostoses: A Current Understanding of Clinical and Genetic Advances

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Background

Osteochondroma is the most common bone tumor seen in children [6,22,59]. This cartilage-capped exostosis is found primarily at the juxta-epiphyseal region of the most rapidly growing ends of long bones [59,78]. The true prevalence is not known since many patients with asymptomatic lesions are never diagnosed. A unique subset of patients, however, suffers from hereditary multiple exostosis (HME), an autosomal-dominant disorder manifested by multiple osteochondromas and frequently associated with characteristic progressive skeletal deformities. Recent advances in understanding the molecular and genetic basis of this condition not only offer hope for patients and families with HME, but also offer clues to the underlying basis for the formation of the human musculoskeletal system.

Historically, John Hunter was perhaps the first to comment on the condition now known as HME. In 1786, he described a patient with multiple exostoses in his Lectures on the principles of surgery [37]. In 1814, Boyer published the first description of a family with HME, and this was followed by Guy’s description of a second family in 1825 [9,32]. Most of the clinical aspects of the disease had been described by the late 1800’s. HME was introduced into the American literature in 1915 by Ehrenfried. In 1943, Jaffe made a significant contribution by further elucidating the pathology of HME and helping to differentiate the disorder from Ollier’s disease [24,38]. As with HME, patients with Ollier’s disease have multiple, benign cartilaginous lesions of bone, but the lesions of Ollier’s disease are enchondromas, located within the tubular bones.

The name “multiple exostoses” was given to the condition by Virchow in 1876 [92]. A number of synonyms have been used for this disorder including osteochondromatosis, multiple hereditary osteochondromata, multiple congenital osteochondromata, diaphyseal aclasis, chondral osteogenic dysplasia of direction, chondral osteoma, deforming chondrodysplasia, dyschondroplasia, exostosing disease, exostotic dysplasia, hereditary deforming chondrodysplasia, multiple osteomatoses, and osteogenic disease [24,35,59]. A related entity known as dysplasia epiphysealis hemimelica, or Trevor’s disease, is a rare disorder in which osteochondromas arise from an epiphysis [88].

HME is most frequently described in Caucasians and affects 0.9 to 2 individuals per 100,000; higher prevalences of the condition have been identified in isolated communities such as the Chamorros of Guam or the Ojibway Indian community of Pauingassi in Manitoba, Canada [6,35,42,56,69,85,94]. These populations have a prevalence of 100 and 1310 per 100,000, respectively [6,42]. Although previously thought to have a male predominance [13,38,78], HME now appears to affect both sexes similarly [69,97].

Clinical Presentation

Patients with HME have multiple cartilage-capped exostoses that may be sessile or pedunculated. Although most commonly located at the periphery of the most rapidly growing ends of long bones, the lesions are also frequently found in the vertebral borders of the scapulae, ribs, and iliac crests [79]. Osteochondromas may occur in the tarsal and carpal bones, however they are often less apparent [76] (Fig. 1). There is only one reported case of an exostosis in the skull; there are no reported cases of lesions arising from the facial bones [35,38].

Exostoses are initially recognized and diagnosed in the first decade of life in over 80% of individuals with HME and are most commonly first discovered on the tibia or scapula as these are often the most conspicuous locations [79]. HME is occasionally diagnosed at birth, but such an early diagnosis is usually the result of a specific search—often in the context of a family history of the disorder. Patients with HME vary considerably as to the size and number of lesions. Some individuals have smaller and fewer lesions that may never become symptomatic. The lesions tend to enlarge while the physes are open proportionate to the overall growth of the patient, and the growth of the osteochondromas usually ceases at skeletal maturity. Lesions have been infrequently reported to spontaneously regress during the course of childhood and puberty [13,21]. Recurrence of an exostosis after surgical excision, although rare, has been observed and may be attributed to incomplete removal of lesions contiguous with the physis in growing
While exostoses are histologically and clinically benign lesions, they can result in a variety of problems. Pain, often from soft tissue trauma over exostoses, and cosmetic concerns are frequent complaints in patients with HME. Additionally, bursa formation and resulting bursitis may occur as a result of the exostoses. The most common deformities seen in HME include short stature, limb-length discrepancies, valgus deformities of the knee and ankle, asymmetry of the pectoral and pelvic girdles, bowing of the radius with ulnar deviation of the wrist, and subluxation of the radial head [69,72,79,97]. Relative shortening of the metatarsals, metacarpals, and phalangeas as well as scoliosis, coxa valga, and acetabular dysplasia have been described less commonly [18,28,39,71]. Associated soft tissue problems include tendon, nerve or vascular impingement, entrapment or injury. Spinal cord compression is also a rare, but well documented, complications of HME [26,63,72,73]. Solomon reported both urinary and intestinal obstruction as other uncommon soft tissue complications [79]. Dysphagia secondary to a ventral cervical exostosis and spontaneous hemothorax as a result of rib exostoses have been described [2,17,23,89]. There have also been reports of exostoses interfering with normal pregnancy and leading to a higher rate of Cesarean sections [46,97].

Individuals with HME are frequently of short stature, with most having heights 0.5 to 1.0 SD below the mean [71,75]. Affected adult males and females have been observed to have heights below the fifth percentile in 36.8% and 44.2% of cases, respectively [97]. Sitting height is generally less abnormal than total height, indicating that the limbs are involved disproportionately as compared to the spine [71].

Limb-length discrepancy is also common. A clinically significant inequality of 2 cm or greater has been reported with a prevalence ranging from 10%–50% [69,71]. Shortening can occur in the femur and/or the tibia; the femur is affected approximately twice as commonly as the tibia [71]. Surgical treatment with appropriately timed epiphysiodesis has been satisfactorily employed in growing patients.

In addition to limb-length discrepancies, a number of lower extremity deformities have been documented. Since the disorder involves the most rapidly growing ends of the long bones, the distal femur is among the most commonly involved sites and 70%–98% of patients with HME have lesions (Fig. 2) [69,71,79]. Coxa valga has been reported in up to 25% [71]; lesions of the proximal femur have been reported in 30%–90% of patients with HME [69,79]. Femoral anteverision and valgus have been associated with exostoses located in proximity to the lesser trochanter [94]. Lesions of the proximal femur can also result impaired hip flexion. There have been at least three reported cases of acetabular dysplasia with subluxation of the hip in patients with HME [28,86]. This results from exostoses located within or about the acetabulum that may interfere with normal articulation.

Valgus knee deformities are found in 8%–33% of patients with HME [56,69,71]. Although distal femoral involvement is common, the majority of cases of angular limb deformities are due mostly to lesions of the proximal tibia and fibula which occur in 70%–98% and 30%–97% of cases, respectively [69,71,79]. The fibula has been found by Nawata et al. to be shortened disproportionately as compared to the tibia, and this is likely responsible for the consistent valgus direction of the deformity [56]. Seven of twenty patients with this valgus deformity in the series by Shapiro et al. required corrective osteotomy [71]. It should be noted that this procedure is associated with appreciable risk due to the proximity of neurovascular structures.

Valgus deformity of the ankle is also common in patients with HME and is observed in 45%–54% of patients in most series [39,71,75]. This valgus deformity can be attributed to multiple factors including shortening of the fibula relative to the tibia (Fig. 3). A resulting obliquity of the distal tibial epiphysis and medial subluxation of the talus can also be associated with this deformity, while developmental obliquity of the superior talar articular surface may provide partial compensation [71]. In more advanced cases, excision of exostoses, alone, does not correct the ankle deformity, although, it may improve preoperative symptoms and cosme-
sis [74]. Early medial hemiepiphyseal stapling of the tibia in conjunction with exostosis excision can correct a valgus deformity at the ankle of 15° or greater associated with limited shortening of the fibula [71,74]. Fibular lengthening has been used effectively for severe valgus deformity with more significant fibular shortening (i.e., when the distal fibular physis is located proximal to the distal tibial physis) [74]. Supramalleolar osteotomy of the tibia has also been used effectively to treat severe valgus ankle deformity [71]. Growth of exostoses can also result in tibiofibular diastasis, which can be treated with early excision of the lesions [80].

Osteochondromas of the upper extremities frequently cause forearm deformities. The prevalence of such deformities has been reported to be as high as 40%–60% [38,69,71,79,100]. Disproportionate ulnar shortening with relative radial overgrowth has been frequently described and may result in radial bowing. Subluxation or dislocation of the radial head is a well-described sequelae in the context of these deformities and was seen in 8 of 37 elbows examined by Shapiro et al. [71] (Fig. 4). Dislocation of radial head has been associated with a loss of pronation, greater ulnar variance, and functional impairment [81]. Disruption of the radioulnar joint, ulnar deviation, and ulnar translocation of the carpus are often associated with HME [27,79]. This complex of deformities, while similar to Madelung’s deformity, does not manifest itself in the characteristic relative elongation or dorsal subluxation of the distal ulna as seen in Madelung’s deformity [65,71].

In 1891, Bessel-Hagen was first to discuss deformities of the forearm in HME and proposed that the irregular eccentric growth of osteochondromas accounted for the loss in longitudinal growth of the bone [5]. This hypothesis was supported by Jaffe, and later by Porter et al., who found that the length of forearm bones inversely correlates with the size of the exostoses [38,62]. Thus, the larger the exostoses and the greater the number of exostoses, the shorter the involved bone. Moreover, lesions with sessile rather than pedunculated morphology have been associated with more significant shortening and deformity [16]. Thus, the skeletal growth disturbance observed in HME is a local effect of benign growth [62].

Accordingly, the disproportionate shortening of the ulna can be generally attributed to two causes: since the distal ulnar physis is responsible for greater longitudinal growth relative to that of the distal radius (85% versus 75%), equal involvement results in more substantial ulnar shortening. Additionally, bones with smaller cross-sectional diameter tend to be shortened more considerably when affected by HME, and so equal involvement of the two bones preferentially affects the ulna which has a diameter of only one-fourth that of the radius. Consequently, radial bowing had been theorized to result from a tethering effect due to the

Fig. 2. (A) Standing A/P radiograph of the lower extremities showing left genu valgum. (B) Standing A/P radiograph demonstrating correction of the femoral deformity with a lateral opening-wedge osteotomy and internal fixation.
relative shortening of the ulna [75,79]. Burgess and Cates, however, disputed this theory with their finding that radial bowing was uncorrelated with measured ulnar shortening in their series of 35 patients, though their study did find a strong correlation between ulnar shortening in excess of 8% and dislocation of the radial head [11].

The degree of forearm involvement in patients with HME has been shown to be strongly associated with the general severity of the disease. Taniguchi classified his patients into three groups: (1) those with no involvement of the distal forearm, (2) those with involvement of the distal radius or ulna without shortening of either bone, and (3) those with involvement of the distal radius or ulna with shortening of either bone. He found that increasing forearm involvement was associated with an earlier age of diagnosis of HME, a greater number of generalized exostoses, shorter stature, a greater number of exostoses affecting the knee, and increased valgus deformity of the ankle. Not surprisingly, all patients with dislocations of the radial head in his series were in the most severely affected group, with shortening in addition to distal exostoses (i.e., group 3) [87].

Many of the deformities of the forearm in patients with HME are amenable to surgical treatment. Indications for surgical treatment include painful lesions, an increasing radial articular angle, progressive ulnar shortening, excessive carpal slip, loss of pronation, and increased radial bowing with subluxation or dislocation of the radial head [99]. In a study of 25 patients who underwent surgery for correction of forearm deformities, Fogel et al. determined that, while early osteochondroma excision alone may decrease or halt progression of forearm deformity, it did not consistently provide full correction. They found that ulnar translocation of the carpals on the distal radius can be corrected by ulnar lengthening, but persistent relative ulnar shortening is likely to recur (Fig. 5). For patients with increased radiocarpal angulation or carpal subluxation, they concluded that osteochondroma excision in conjunction with distal radial osteotomy or hemiepiphysial stapling resulted in improved function and cosmesis [29]. Wood et al. noted that such surgeries of the distal forearm result in only modest improvement of function, but they felt, significant improvement in cosmesis [100].

Complete dislocation of the radial head is a serious progression of forearm deformity and can result in pain, instability, and decreased motion at the elbow. Surgical intervention should be considered to prevent this from occurring. When symptomatic, this can be treated in older patients with resection of the radial head [53,71]. Surgical relocation of the radial head, however, has not consistently proven to be successful [100].

Hand involvement in HME has been reported in 30%–79% of patients [69,79]. Fogel et al. observed metacarpal involvement and phalangeal involvement in 69% and 68%,
respectively, in their series of 51 patients [29]. In their series of 63 patients, Cates and Burgess found that patients with HME fall into two groups: those with no hand involvement and those with substantial hand involvement averaging 11.6 lesions per hand [18]. They documented involvement of the ulnar metacarpals and proximal phalanges most commonly with the thumb and distal phalanges being affected less frequently. While exostoses of the hand resulted in shortening of the metacarpals and phalanges, brachydactyly was also observed in the absence of exostoses [18]. In most series, the majority of patients were asymptomatic [18,71]. In Cates and Burgess’s study, no angular deformities of the digits were observed, and only 4 of 22 patients with hand involvement required surgery [18].

Both neurologic and vascular problems can arise throughout the extremities as complications of HME. Wicklund et al. reported peripheral nerve compression symptoms in 22.6% of patients in their series of 180 [97]. Peroneal neuropathy associated with exostoses of the proximal fibula in children is a recognized complication [14,47]. At our institution, six children were described with peroneal nerve palsy associated with osteochondromas of the proximal fibula [14]. Ulnar neuropathy secondary to compression by an exostosis of the elbow has also been described [68].
Wicklund et al. reported the general prevalence of vascular compression secondary to exostoses to be 11.3% [97]. In their review of vascular complications stemming from osteochondromas, Vasseur et al. reported 97 cases, of which 71 were sporadic osteochondromas while 26 were associated with HME [91]. Pseudoaneurysm, vascular compression, arterial thrombosis, aneurysm, and venous thrombosis were the most commonly reported, while claudication, acute ischemia, and phlebitis were found to be the most commonly associated clinical presentations. In Vasseur et al.’s series, 83% of vascular problems were located in the lower extremity, and the popliteal artery was the most frequently injured artery [91]. Appropriate, and usually urgent, surgical treatment of these patients is required in this setting.

Malignant transformation of a benign osteochondroma to a chondrosarcoma or other sarcoma is another complication of HME. Fortunately, most chondrosarcomas in this setting are low grade and can be treated with wide excision. Patients with such lesions usually present with a painful mass. Rarely, nerve compression can be the presenting complaint [58]. Ochsner published a report of 59 patients with HME who had malignant transformation. The mean age at diagnosis of malignancy was 31 years of age with malignant degeneration seldom occurring in the first decade or after the fifth decade of life [57]. The reported incidence of malignant degeneration is highly variable, ranging from 0.5%–25% [30,77,94]. This disparity can be attributed not only to a possible selection bias inherent for a tertiary referral center, but also to the inability to detect all HME patients without malignant degeneration, thus making it difficult to determine the true denominator [16]. More recent studies estimate the rate of secondary malignancy to be 5% or less [6,31,46,69,94]. The risk of malignant transformation may vary among families reflecting genetic heterogeneity predisposing to malignant degeneration [69]. Because of this risk, patients with HME should be followed carefully to detect early sarcomatous transformation. Growth of a lesion after skeletal maturity should raise a suspicion of malignant degeneration [69]. Appropriate, and usually urgent, surgical treatment of these patients is required in this setting.

Genetic Basis of Disease

One of the early studies that looked at the hereditary characteristics of patients with HME was done by Stocks and Barrington in 1925 [84]. Since that time, it has been determined that HME is an autosomal dominant disorder with near complete penetrance [35,78,97]. HME is a genetically heterogeneous disorder and has been associated with mutations in at least three different genes, termed EXT genes. At least two of these genes are thought to function as tumor suppressor genes. The three described EXT loci have been recently mapped: EXT1 on chromosome 1p36 [99], EXT2 on 1p11-p12 [107], and EXT3 on 8p12-p22 [90]. Unlike EXT1 and EXT2, the EXTL proteins are more variable in size. They do however, share characteristic features with the EXT gene family such as conserved biologically active sequences. Most notably, EXT2 has been demonstrated to be a transferase involved in the biosynthesis of heparin sulfate and likely encodes the crucial enzyme, which initiates heparan sulfate synthesis [41].

EXT1 and EXT2 function as tumor suppressor genes encoding homologous glycoproteins of similar size (746 and 718 amino acids, respectively) and structure which are expressed ubiquitously throughout the musculoskeletal system [1,82,109]. Both glycoproteins are glycosyltransferases that function in the biosynthesis of heparan sulfate [52]. They are located in the membrane of the endoplasmic reticulum and have a role in modifying and enhancing the synthesis and expression of heparan sulfate, a complex polysaccharide that has been implicated in a variety of cellular processes including cell adhesion, growth factor signaling, and cell proliferation [15,101].

Wuyts and Van Hul proposed a model for the development of exostoses based upon a mutation in the EXT gene [105]. They note that the function of the EXT gene may be better understood by studying the tout-velu gene, the drosophila homologue of EXT1. The tout-velu gene has been implicated in the normal diffusion of hedgehog (hh), a signaling protein [4]. Among the mammalian homologues of hedgehog is Indian hedgehog (Ihh), a regulator of cartilage differentiation. Indian Hedgehog is expressed by chondrocytes and then diffuses into the perichondrium. There, it exerts its influence by inhibiting further differentiation of additional chondrocytes [93]. Wuyts and Van Hul offer a mechanism of exostosis formation in which a mutation in the EXT gene disrupts Indian hedgehog diffusion, in turn, inhibiting the negative feedback loop present in chondrocyte differentiation and resulting in abnormal skeletal development [105]. Thus, a mutation in the EXT gene may disrupt normal cartilage growth resulting in the formation of an osteochondroma.

Three other homologous genes, termed EXT-like genes, have been identified: EXTTL1 on chromosome 1p36 [99], EXTTL2 on 1p11-p12 [107], and EXTTL3 on 8p12-p22 [90]. Unlike EXT1 and EXT2, the EXTL proteins are more variable in size. They do however, share characteristic features with the EXT gene family such as conserved biologically active sequences. Most notably, EXT2 has been demonstrated to be a transferase involved in the biosynthesis of heparin sulfate and likely encodes the crucial enzyme, which initiates heparan sulfate synthesis [41]. While EXT2 has been implicated in the same pathway as EXT1 and EXT2, its role in the formation of exostoses remains to be proven [105].

HME can also be associated with certain other genetic syndromes. While the EXT phenotype resulting from small insertions, deletions, and point mutations is limited to the growth of exostoses, more substantial deletions involving the EXT1 or EXT2 genes in addition to other adjacent genes can result in continuous gene syndromes. Such syndromes are caused by larger deletions which inactive several genes in the germline. Multiple exostoses are seen in patients with
Langer-Giedion syndrome (LGS), or tricho-rhino phalangeal syndrome type II (TRPII), and DEFECT 11 syndrome. Along with exostoses due to the deletion of the EXT1 gene, patients with TRPII commonly display mental retardation, cone-shaped epiphyses, and atypical facies [43]. This syndrome is caused by deletion of the yet to be mapped TRPI gene which is located proximally to the EXT1 locus [49,50]. DEFECT 11 syndrome is seen in patients with deletions including the entire EXT2 gene on chromosome 11p11-p12. This syndrome is comprised of exostoses in addition to enlarged parietal foramina, craniofacial dysostosis, and mental retardation [3,48,103].

Both EXT1 and EXT2 hereditary multiple exostoses pedigrees exhibit germline mutations in the EXT gene that consist primarily of loss-of-function mutations, often resulting in premature stop codons [1,19,60,83,109]. These mutations result in truncated proteins with decreased biological activity. Further examination shows that in both sporadic and inherited exostoses, chromosomal deletions are present surrounding the EXT1 and EXT2 loci [54]. Additionally, the EXT-like genes are located at sites of tumor suppressor genes in neoplasia; EXT1 has been localized to 1p36, which is often a site of deletion in tumors, and EXT3 may be a breast cancer locus [90,99].

As further evidence for a role in tumor suppression, a number of studies have demonstrated loss of heterozygosity (LOH) at the EXT loci in the cartilaginous cap of osteochondromas and tissue from chondrosarcomas [7,8,33,34,66]. Clonal karyotypic abnormalities have also been documented in osteochondromas [10,54]. Taken together, these studies indicate that the cartilaginous portion of the osteochondromas has a clonal or neoplastic origin [8]. Porter and Simpson then contend that the ‘osteal’ portion of the osteochondroma functions as reactive or supportive stroma since it has been observed that surgical ablation of the cartilage cap alone prevents continued growth of the osteochondroma has a clonal or neoplastic origin [8].

Porter and Simpson then contend that the ‘osteal’ portion of the osteochondroma functions as reactive or supportive stroma since it has been observed that surgical ablation of the cartilage cap alone prevents continued growth of the lesion [62]. There is currently, however, no molecular or immunohistochemical data which supports this observation [8].

As evidence for a genetic progression model of tumor formation, osteochondroma occurrence in HME requires inactivation of both copies of the EXT1 gene in cartilaginous cells [8,9,36]. It remains unclear whether this complete inactivation also occurs in sporadic osteochondromas [8]. The process of malignant transformation to a peripheral chondrosarcoma from a benign precursor may require additional genetic alterations. Additionally, there exists some evidence that carcinogenesis may be associated with deletions found in osteosarcoma and in multiple endocrine neoplasia [61]. Aggressive chondrosarcomas have also been associated with p53 tumor suppressor gene deletions [66]. The genetic changes which accompany malignant transformation require further study before the true mechanism is fully understood.

Pathogenesis

Although the true pathogenesis of HME is not fully understood, many theories have been proposed. Isolation of cartilaginous islets from the diaphyseal surface of growing cartilage had been hypothesized to cause abnormal osteogenesis. Further, physical stress at sites of tendon attachment had also been thought to convert focal accumulations of embryonic connective tissue to hyaline cartilage. Anatomical theories have attributed osteochondroma formation to a defect in the anchoring of germinal cartilage cells to the physeal plate or to a failure of a thin cortical sleeve of bone acting as a structural constraint allowing a spill-over of physis cells onto the metaphysis [40,61,64,79].

Theories of pathogenesis still exist which remain consistent with a clonal etiology. Müller theorized that osteochondromas result from a primary defect in peristomal differentiation in which ectopic collections of cartilage cells arise from the proliferative layer of the metaphyseal peristomeum [38,55]. Osteochondromas have also been thought to arise from multipotent mesenchymal cells in the region of the perichondrial groove of Ranvier [12,70], or, according to Langenskiöld, from proliferative interstitial physis cartilage that persist in chondrogenesis as they are transformed into the proliferative layer of the metaphyseal peristomeum [44].

Conclusions

In order to better understand HME, additional research is required. It still remains unclear as to why EXT expression is so widespread in human tissues, yet only inactivation at specific sites results in defects. Additionally, the role of impaired heparan sulfate expression will need to be further explored so that the pathogenesis of the disorder can be determined. The EXT3 gene remains to be fully characterized along with other genes possibly involved in HME, and functional analysis of these genes, in addition to the EXT1 and EXT2 genes already identified, is an area of current research [19,51,83]. The genotypic-phenotypic relationship in HME is also being actively investigated [16]. While much has already been learned about HME, further elucidation of the genetic basis and pathogenesis holds promise for better prediction of prognosis and treatment, and, perhaps, may provide additional information about the mechanisms and secrets of normal limb development or other musculoskeletal disorders.

References

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