

Hereditary Multiple Exostoses: A Comprehensive Clinical Overview

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INTRODUCTION

Hereditary Multiple Exostoses (HME), also known as multiple osteochondromas or diaphyseal aclasis, is a rare autosomal dominant skeletal disorder characterized by the formation of multiple benign cartilage-capped bone tumors (osteochondromas) that grow outward from the metaphyses of long bones [1,2].

HME is classified as a rare disease, with an estimated prevalence of approximately 1 in 50,000 individuals in the general population, though this figure likely represents an underestimate due to variable penetrance and underdiagnosis of mildly affected individuals [3,4]. The condition demonstrates worldwide distribution with no significant ethnic or racial differences and has been documented across Europe, Asia, Africa and the Americas [5].

HME affects both sexes, with some reports suggesting a slight male predominance that may reflect ascertainment bias [2,6]. Diagnosis in both boys and girls typically occurs during childhood, as osteochondromas become clinically apparent through palpable masses, skeletal deformities, or incidental radiographic findings [7].

The majority of HME cases follow an autosomal dominant inheritance pattern, although some arise from de novo mutations [8]. The condition results from loss-of-function mutations in the *EXT1* and *EXT2* genes, coding for a complex that is crucial for the polymerization of heparan sulfate in the skeletal system [9,10]. This process allows for regulation of chondrocyte differentiation, ossification, and apoptosis [11]. Disordered expression of these genes leads to tumor formation in HME. Mutations in *EXT1* and *EXT2* together account for nearly all identified genetic cases of HME, with *EXT1* generally more frequent than *EXT2* [10].

A small percentage of patients with clinical HME do not have identifiable mutations in either gene [12]. Patients with *EXT1* mutations tend to have more severe phenotypes with greater numbers of exostoses and higher rates of complications compared to those with *EXT2* mutations [2].

Here we provide a summary of the clinical presentation of HME, as well as details on how it is diagnosed and managed.

HME has a variety of clinical manifestations, which affect quality of life

Clinical manifestations vary widely, from minimal symptoms to significant skeletal deformities and functional limitations [13]. The following symptoms represent the most significant contributors to decreased quality of life in HME patients:

Chronic pain: Chronic pain represents the most frequently reported symptom in HME [14,15]. Pain arises from multiple mechanisms including mechanical irritation of surrounding soft tissues, nerve compression, bursa formation over prominent exostoses and muscle strain from altered biomechanics [16]. The persistent nature of pain significantly impacts daily functioning, sleep quality, and psychological well-being. Pain intensity varies considerably among patients but often worsens with physical activity and skeletal growth spurts during childhood and adolescence [14].

Functional limitations and reduced range of motion: Skeletal deformities and strategically located osteochondromas frequently result in restricted joint mobility and functional impairment [17,18]. Common deformities include forearm abnormalities, such as radial head dislocation and ulnar shortening, ankle valgus deformity, and limb length discrepancies [19,20]. These

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limitations affect activities of daily living, participation in recreational activities, and occupational capacity. Studies using validated outcome measures demonstrate that HME patients score significantly lower than healthy controls on physical function subscales of quality-of-life assessments [15].

Skeletal deformities and short stature: Progressive skeletal deformities are common in HME patients and substantially impact both physical function and psychological well-being [2,21]. Asymmetric growth disturbances can produce limb length discrepancies, angular deformities and joint incongruity. Disproportionate short stature is common, with adult height often falling below expected genetic potential based on parental height [22]. The visible nature of skeletal deformities contributes significantly to body image concerns, social anxiety and reduced self-esteem, particularly during adolescence [23].

Nerve and vascular compression syndromes: Compression of adjacent neurovascular structures by expanding osteochondromas affects 11-30% of patients and can produce severe symptoms including paresthesias, weakness and vascular compromise [24,25]. Common compression syndromes include peroneal nerve palsy, ulnar nerve compression, and rarely, spinal cord compression when exostoses arise from vertebral elements [26]. Vascular complications, though less frequent, can include arterial stenosis, pseudoaneurysm formation and venous thrombosis [27]. These complications often require urgent surgical intervention and can result in permanent neurological deficits if not promptly addressed [28].

Psychological distress and reduced quality of life: The cumulative burden of chronic pain, functional limitations, visible deformities, and concerns about malignant transformation produces significant psychological impact, with studies documenting elevated rates of anxiety and depression in HME

patients compared to healthy controls [23,29]. Quality-of-life assessments consistently demonstrate impairment across physical, emotional and social domains [15]. Children with HME report increased school absence, reduced participation in peer activities, and heightened parental concern [30]. The hereditary nature of the condition adds additional stress related to guilt about transmission and decisions regarding family planning [31].

There are several routes to an HME diagnosis

The diagnosis of HME integrates clinical evaluation, radiographic assessment, and genetic testing, with the diagnostic approach evolving as clinical suspicion increases and complications are evaluated [32].

Initial clinical evaluation: Diagnosis typically begins when patients present with palpable bony masses, skeletal deformities, growth disturbances, or pain during childhood [7]. A comprehensive clinical examination should assess for multiple osteochondromas, characterize their location and size, evaluate for skeletal deformities and limb length discrepancies and assess joint range of motion and neurovascular function [33]. A detailed three-generation family history is essential, as approximately 62% of cases demonstrate familial inheritance [8].

Radiographic imaging: Plain radiography remains the primary imaging modality for initial diagnosis and surveillance, effectively demonstrating the characteristic features of osteochondromas including bony stalks arising from metaphyses, continuity between lesion and underlying bone and in some cases, visible cartilage caps (though calcification may be required for radiographic visibility) [34,35]. An example of a radiograph image is provided in (Figure 1-4). Complete skeletal surveys are often performed at initial diagnosis to document the full extent of disease and establish a baseline for comparison [36].



Figure 1: Standing radiograph of bilateral lower legs. **Note:** There are large osteochondromas visualized on the proximal fibulas, proximal tibias, as well as the distal tibias and fibulas of both legs. There are guided growth plates at the left medial distal femur and medial proximal tibia. Additionally, at the ankles there is proximal migration of the fibula due to the tethering effects of the distal tibia-fibula osteochondromas resulting in ankle valgus.

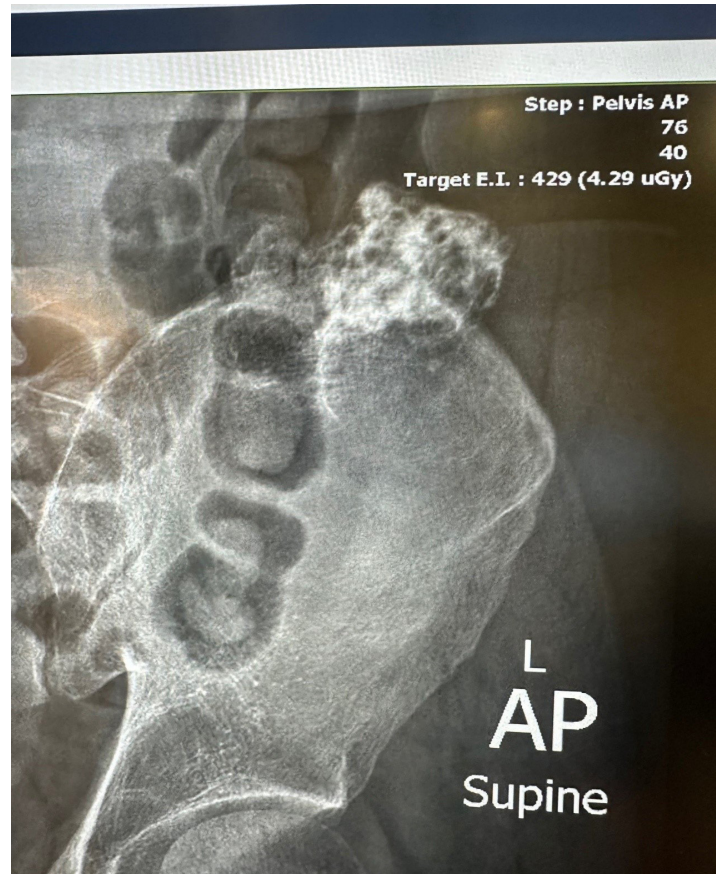


Figure 2: Radiograph of a large osteochondroma of the left iliac wing.



Figure 3: Oblique view from a pelvic Computed Tomography (CT) with 3D reconstruction of a left iliac wing osteochondroma.



Figure 4: Sagittal view from a pelvic (Computed Tomography) CT with 3D reconstruction of a left iliac wing osteochondroma.



Figure 5: Tenting of the peroneal nerve over the top of a proximal fibula osteochondroma.

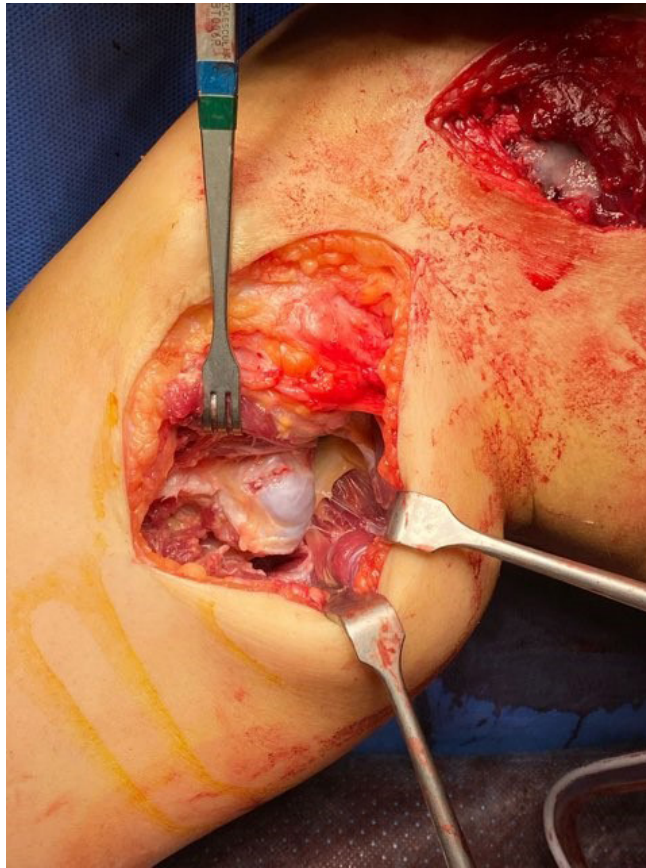


Figure 6: Proximal fibula osteochondroma has been exposed. **Note:** The nerve has been mobilized and now runs posterior to the osteochondroma.

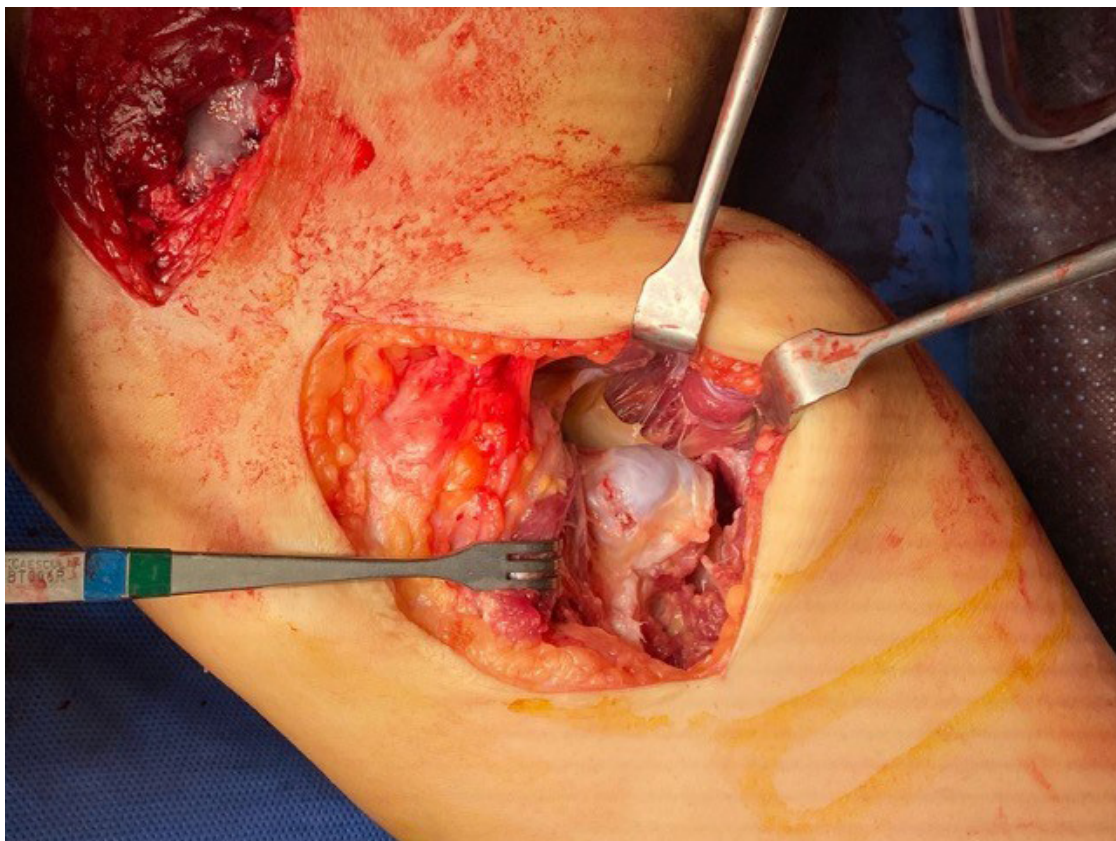


Figure 7: The peroneal nerve has been decompressed as it runs into the lateral and anterior compartments of the leg. The nerve continues to be displaced and compressed by the large osteochondroma on the fibular head.



Figure 8: Excised osteochondroma with shiny cartilage cap.

Advanced imaging with Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) is reserved for specific clinical scenarios including evaluation of suspected malignant transformation (cartilage cap thickness >2 cm in adults suggests increased malignancy risk), assessment of spinal or pelvic lesions where plain radiography is limited, preoperative planning for complex lesions, and evaluation of neurovascular complications [37,38]. Whole-body MRI has emerged as a valuable tool for comprehensive disease assessment and surveillance, particularly in research settings [39]. An example of 3-Dimensional (3D) deconstruction is illustrated in (Figures 3,4).

Genetic testing: Molecular genetic testing for *EXT1* and *EXT2* mutations provides diagnostic confirmation and enables accurate genetic counseling [10]. Testing is particularly useful when clinical and radiographic findings are unclear, for confirming diagnosis in mildly affected individuals, and for family planning and counseling [40,41].

Current testing strategies typically employ next-generation sequencing panels that can detect both sequence variants and large deletions/duplications, achieving detection rates of approximately 85-95% in patients with clinical HME [11,42]. The inability to identify mutations in all clinically affected individuals suggests either genetic heterogeneity or limitations in current testing methodologies [12].

Differential diagnosis: Several conditions may mimic HME and require consideration, including metachondromatosis (distinguished by enchondromas in addition to exostoses), Langer-Giedion syndrome (characterized by additional features including intellectual disability and distinctive facial features) and solitary osteochondroma (single lesion without genetic basis) [43,44]. Clinical context, family history, and genetic testing help differentiate these entities [45]. Clinical evaluation and

genetic testing usually allow confident distinction among these conditions.

HME management requires a multidisciplinary approach

The multidisciplinary approach for managing HME requires addressing the skeletal manifestations as well as the functional, psychological and genetic counseling needs of patients and families [46,47]. Currently, no disease-modifying pharmacological therapy exists for HME and treatment remains primarily supportive and surgical [48].

Conservative management: Conservative approaches form the foundation of HME management for asymptomatic or minimally symptomatic lesions. These strategies include regular clinical and radiographic surveillance to monitor disease progression and detect complications early, with regular clinical examinations during growth. Imaging is pursued as indicated by symptoms or changes, rather than by rigid protocol [49,50].

Physical therapy plays a crucial role in maintaining joint mobility, strengthening compensatory muscle groups, addressing biomechanical abnormalities and providing gait training [51]. Pain management utilizes multimodal approaches including Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), physical modalities (heat, ice, transcutaneous electrical nerve stimulation), and in select cases, referral to pain management specialists for chronic pain syndromes [52].

Orthotic devices may benefit certain patients through shoe lifts for limb length discrepancies, ankle-foot orthoses for ankle instability, and custom orthotics to address biomechanical abnormalities [53,54].

Surgical intervention: Surgical excision of osteochondromas is the definitive treatment for symptomatic lesions. Surgical

images are provided in (Figures 5-11). Clear indications for surgery include significant pain unresponsive to conservative management, functional limitation from joint restriction or deformity, neurovascular compression, suspected malignant transformation, rapid growth or change in lesion characteristics and significant psychological impact related to appearance [55].

Surgical procedures vary based on lesion location, size and

associated complications. Simple excision of pedunculated or sessile osteochondromas is most common, while corrective osteotomies may be necessary for angular deformities and limb length discrepancies [19]. More complex reconstructive procedures address joint incongruity and severe deformities, with some patients requiring guided growth techniques in skeletally immature patients [56,57].



Figure 9: Exposure of osteochondroma left iliac wing.

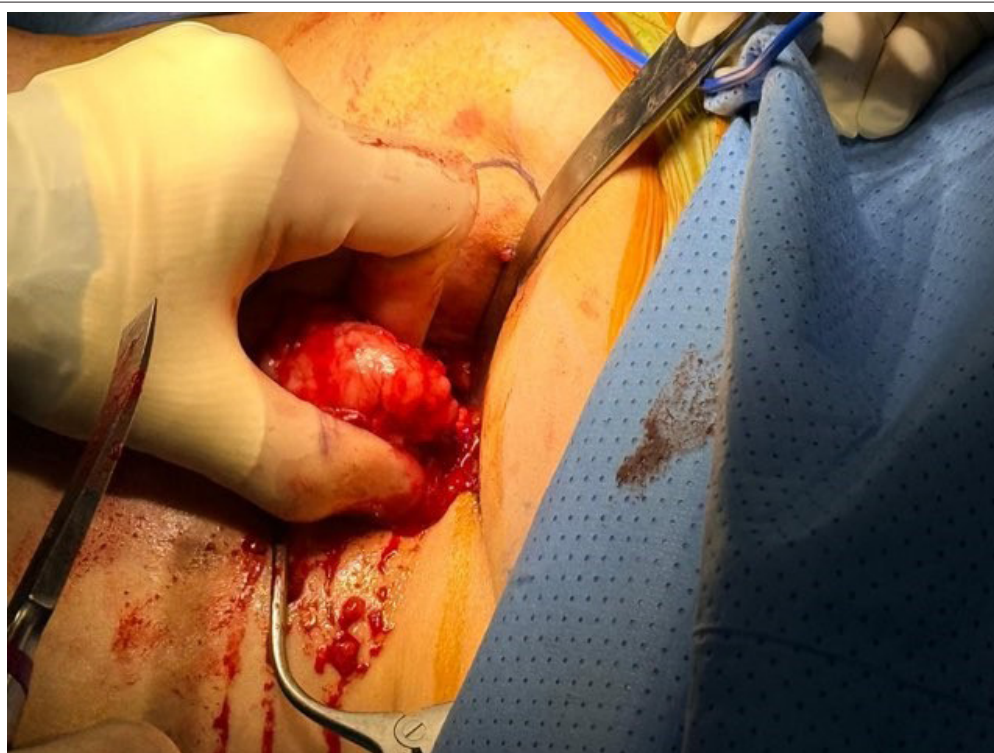


Figure 10: Surgical removal osteochondroma left iliac wing.



Figure 11: Osteochondroma of left iliac wing surgically removed.

Surgical outcomes are generally favorable for well-selected cases, with most patients experiencing symptomatic improvement [58]. However, recurrence can occur, particularly in young children with significant remaining growth potential, and multiple surgeries throughout childhood and adolescence are common [59]. Surgical complications include typical orthopedic surgical risks (infection, bleeding, neurovascular injury), incomplete resection leading to recurrence and iatrogenic growth plate injury in skeletally immature patients [60].

Management of malignant transformation: Malignant transformation is estimated to occur in 0.5 to 5 percent of HME patients [1,6,61]. The development of secondary peripheral chondrosarcoma represents a serious complication requiring prompt recognition and aggressive treatment [62,63]. Warning signs include pain in a previously asymptomatic lesion, rapid increase in lesion size after skeletal maturity, and cartilage cap thickness exceeding 2 cm on imaging in adults [37].

Management involves wide surgical excision with clear margins as the primary treatment, with adjuvant chemotherapy and radiation therapy considered based on tumor grade, stage and surgical margins [64]. Prognosis depends on early detection and complete surgical resection, with lower-grade tumors having favorable outcomes following adequate surgical treatment [65].

CONCLUSION

Hereditary multiple exostoses is a complex genetic disorder that significantly impacts patients physical function, psychological well-being, and quality of life. While genetic testing has clarified the molecular basis through identification of *EXT1* and *EXT2* mutations, no disease-modifying therapies currently exist and

treatment remains primarily supportive and surgical. Successful management requires a multidisciplinary approach addressing orthopedic complications, chronic pain, functional limitations and psychological burden. Early diagnosis enables appropriate surveillance for complications, particularly malignant transformation, and facilitates genetic counseling for affected families. Coordinated care focusing on symptom management, timely surgical intervention and comprehensive psychosocial support remains essential for optimizing outcomes in individuals living with HME.

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