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Review Article

Orthopaedics Section

Hereditary Multiple Exostoses: A Narrative Review of Clinical Spectrum, Molecular Pathogenesis, Diagnostic Advances, and Emerging Therapeutic Approaches

SHASHANK YADAV[1], RATNAKAR AMBADE[2], NEELAKSH[3], KRISHNA SAMBARE[4], BHAGYESH SAPKALE[5]

ABSTRACT

Hereditary Multiple Exostoses (HME), also known as multiple osteochondromas, is a rare autosomal dominant skeletal disorder characterised by multiple benign cartilage-capped bony outgrowths that develop along the metaphyses of long and flat bones. Clinically, HME presents as palpable lesions, which are usually painless, but complications such as mechanical pain, skeletal deformities, joint restriction, neurovascular compression, and, rarely, malignant transformation to chondrosarcoma can occur. Classical radiography remains the first-line diagnostic tool, while advanced imaging modalities, including Magnetic Resonance Imaging (MRI), Computed Tomography (CT), whole-body MRI, and PET/CT, are used to detect complex lesions and early signs of malignancy. Uncertain cases can be confirmed by molecular analysis of EXT1/EXT2 genes and Next-Generation Sequencing (NGS). Treatment is largely symptomatic and includes surveillance, surgical resection, and corrective orthopaedic procedures for deformities. Emerging disease-modifying agents, such as palovarotene and heparanase inhibitors, may alter osteochondroma formation, as suggested by preclinical trials. This narrative review summarises current knowledge on the clinical spectrum of HME, its pathogenesis, diagnostic methods, treatment options, and emerging therapeutic approaches.

Keywords: Bony deformities, Cartilage cap, Genetic mutation, Neurovascular compression, Surveillance

INTRODUCTION

HME, or multiple osteochondromas, is a rare genetic skeletal disorder characterised by multiple benign cartilage-capped bony outgrowths (osteochondromas) arising from the metaphyseal regions of long or flat bones [1]. These lesions are usually asymptomatic but can cause mechanical effects, including local pain, restricted joint motion, limb deformities, neurovascular compression, or growth abnormalities [1,2]. A major clinical concern is the risk of malignant transformation into chondrosarcoma, which occurs in approximately 1–10% of HME cases—significantly higher than the risk associated with solitary osteochondroma [3].

The syndrome of multiple osteochondromas has been recognised clinically for over a century, although its hereditary nature and underlying pathophysiology have been gradually elucidated [4]. Historical orthopaedic and pathology texts described patients with multiple bony protuberances around long bone growth plates, often accompanied by limb deformities or growth anomalies [4,5]. Over time, the condition has been referred to in the literature by various names, including diaphyseal aclasis, osteochondromatosis, and multiple cartilaginous exostoses [5].

Modern clinical descriptions of HME date back more than 200 years, with Hunter (1786) and Boyer (1814) providing early reports of the disorder [6]. In 1915, Ehrenfried reviewed over 600 cases worldwide in a publication titled Hereditary Deforming Chondrodysplasia – Multiple Cartilaginous Exostoses, marking a significant milestone in defining HME as a distinct entity [7]. Later, systematic studies of HME's natural history were conducted. Schmale GA et al., (1994) reported on a Washington State patient database, providing insight into penetrance, sex ratio, and complication rates [8]. Wicklund CL et al., (1995) followed 43 probands and 137 relatives, reporting on risks of short stature, skeletal deformities, and malignant transformation. They estimated the malignancy rate at approximately 2.8% and stated that penetrance is effectively 100% [9]. These early epidemiologic observations laid the groundwork for subsequent genotype–phenotype and mechanistic studies [8,9].

The identification of germline mutations in the EXT1 and EXT2 genes, which encode heparan sulfate–producing glycosyltransferases, has provided critical insight into the genetic and biochemical pathogenesis of HME [10]. The estimated incidence of HME is approximately 0.9–2 per 100,000 individuals, with a prevalence of about 1 per 50,000 [11,12]. Although HME occurs worldwide, most epidemiologic studies have been conducted in Europe and North America, with additional reports from Africa and Asia, including familial cases in Nigeria and India, highlighting its global distribution [11,12].

This review aims to provide a comprehensive overview of HME, including its clinical spectrum, pathogenesis, diagnostic innovations, and emerging therapies, offering a critical synthesis for clinicians and researchers.

Genetic and Clinical Classification of Hereditary Multiple Exostoses (HME)

HME is primarily classified according to the underlying genetic mutation. The two major genetic types are Type 1 and Type 2, resulting from mutations in the EXT1 gene located on chromosome 8q24 and the EXT2 gene located on chromosome 11p11-p13, respectively [13]. A third locus, referred to as EXT3, has been proposed on chromosome 19p, but it remains less well characterised [13]. This genetic classification has both molecular and prognostic significance [13].

Several studies have indicated that patients with EXT1 mutations tend to exhibit a more severe skeletal phenotype, including a higher number of exostoses, more limb deformities, and greater functional impairment compared with patients carrying EXT2 mutations [10,13,14]. These genetic variants impair heparan sulfate (HS) biosynthesis, which disrupts endochondral ossification, leading to the formation of osteochondromas [14]. Therefore, genetic

classification is a valuable tool for understanding disease severity, predicting complications, and providing guidance on inheritance and prognosis to affected families [13,14].

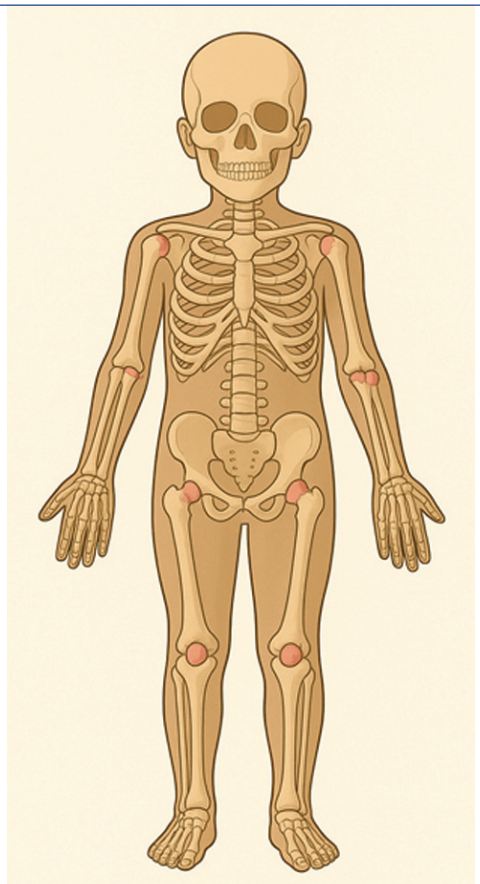
In addition to genetic classification, HME can also be classified clinically based on the degree of skeletal deformity and functional impairment, as proposed by Mordenti M et al., (2013) [15]. According to this system, HME is divided into three main classes:

- Class I: Patients without deformities or functional limitations.
- Class II: Patients with deformities but preserved function.
- Class III: Patients with deformities and significant functional impairment.

Each class is further subdivided into A and B, depending on whether involvement is limited to a single anatomical region (A) or multiple regions (B) [15]. This classification provides a practical framework for assessing disease severity in clinical practice, guiding treatment planning, rehabilitation, and follow-up. It also allows clinicians to standardise reporting, stratify patients for outcome studies, and complement the genetic classification system [15].

Clinical Features and Manifestations of Hereditary Multiple Exostoses (HME)

HME usually manifests during childhood or adolescence, when the metaphyses of long and flat bones give rise to multiple cartilage-capped bony protrusions (osteochondromas) [16]. These lesions are typically painless, firm, and palpable adjacent to joints, detectable through physical examination and imaging [Table/Fig-1] [16]. However, a significant proportion of patients develop pain, usually due to mechanical irritation, bursitis, or compression of adjacent soft-tissues such as muscles, tendons, or nerves [10,17].



[Table/Fig-1]: Representative illustration of Hereditary Multiple Exostoses (HME) showing multiple cartilage-capped bony protrusions (osteochondromas) arising from the metaphyseal regions of long bones; Source- (Self-made by Authors).

In addition to pain and palpable exostoses, skeletal deformities and functional impairment are common [10]. Progressive angular deformities (e.g., knee or ankle valgus), limb length discrepancies, short stature, forearm bone bowing with ulnar shortening, and radial head subluxation may result from disruption of normal growth by osteochondromas [18]. These deformities can limit joint motion and predispose patients to early osteoarthritic changes in adjacent joints [18]. In severe cases, bony growths may compress neurovascular bundles, causing limb ischaemia, paresthesia, or, rarely, spinal cord compression and neurological deficits [4,19].

Osteochondromas affecting the scapula, particularly the ventral side, may produce distinctive mechanical symptoms such as pseudo-winging of the scapula, snapping during shoulder motion, and restricted scapulothoracic movement [20,21]. In some cases, scapular deformities may be noticeable even in the absence of pain [20]. Lesions affecting intercostal nerves or ribs can cause neuralgic pain [20], and large exostoses posterior to the scapula have been associated with bursitis, presenting as painful, rapidly enlarging masses complicating chest wall lesions [22].

An emerging pattern in HME is visceral or mediastinal invasion by osteochondromas, which can compress internal organs or spaces [23]. A recent case report by Yang Z et al., described a patient with HME presenting with an anterior mediastinal mass (osteochondroma/chondrosarcoma) compressing the right ventricle, despite the absence of typical symptoms such as chest pain, cough, or dyspnea [23].

Classical and emerging clinical manifestations of HME are summarised in [Table/Fig-2] [4,10,16-23].

Molecular Pathogenesis of Hereditary Multiple Exostoses (HME)

HME is an autosomal dominant disorder primarily caused by loss-of-function mutations in EXT1 or EXT2, which encode glycosyltransferases required for the polymerisation of heparan sulfate (HS) chains [14]. These EXT proteins work collaboratively in the Golgi apparatus to catalyse the successive addition of N-acetylglucosamine and glucuronic acid units, producing HS chains that are key components of the cell surface and extracellular matrix proteoglycans [14,24]. HS chains mediate the diffusion, gradient formation, and signaling activity of various growth factors, including FGFs and BMPs, during skeletal development [25]. Mutations in EXT1/EXT2 lead to HS deficiency, thereby disrupting these signaling pathways [24,25].

The established model of osteochondroma formation—the characteristic cartilage-capped bony outgrowths in HME—follows a two-hit hypothesis. In addition to the germline heterozygous EXT mutation, inactivation of the wild-type allele in a subset of chondrocytes or perichondrial progenitor cells leads to a localised decrease in HS production [26]. This local deficiency disrupts the balance between antichondrogenic signals (e.g., FGF/ERK) and prochondrogenic signals (e.g., BMP), favouring ectopic cartilage differentiation at the perichondrial border. This results in cartilage nodules and subsequent ossification into osteochondromas [27].

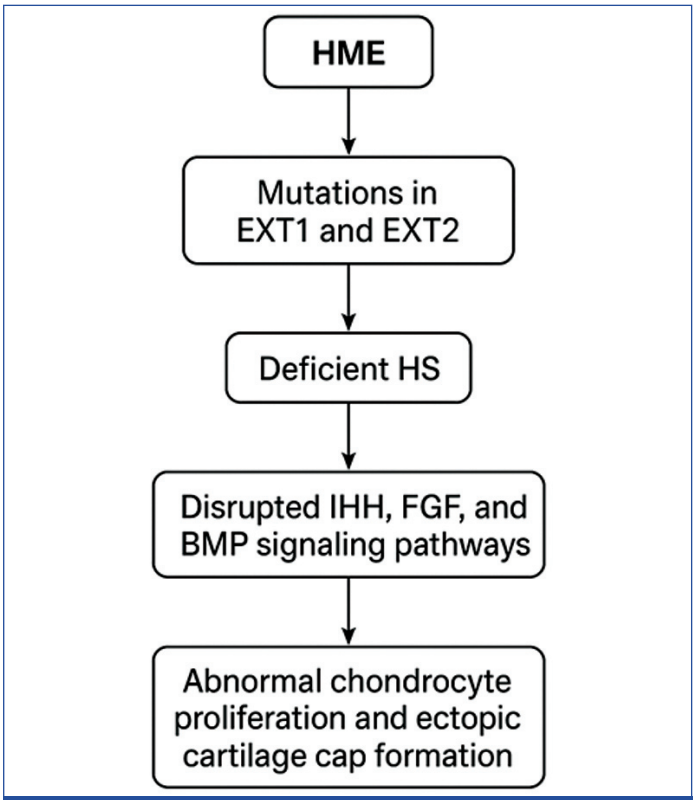
Mouse model studies support this mechanism, showing that selective EXT1 inactivation in a subset of chondrocytes leads to osteochondroma formation and bone deformities that closely mirror those seen in humans [28]. Therefore, the molecular pathogenesis of HME involves HS deficiency, dysregulation of developmental signaling in the growth plate, abnormal cartilage proliferation, and exostosis formation [24]. The molecular pathways and downstream effects of HS deficiency in HME are summarised in [Table/Fig-3].

Differential Diagnosis and Genetic Distinction from Related Skeletal Disorders

Differential diagnosis of HME includes conditions characterised by multiple bone-cartilage outgrowths or enchondromas. For example, Ollier disease and Maffucci syndrome (enchondromatosis) are non inherited disorders featuring intraosseous cartilaginous tumours (enchondromas) rather than exophytic osteochondromas. These

Category	Site/ involvement	Clinical features and description	References
General presentation	Long and flat bone metaphyses	Onset in childhood or adolescence; multiple cartilage-capped bony projections (osteochondromas); firm, palpable, and usually painless masses near joints detected on physical or imaging evaluation.	[16]
Pain and local symptoms	Adjacent soft-tissues (muscles, tendons, nerves)	Pain occurs due to mechanical irritation, bursitis, or compression of surrounding soft-tissue structures.	[10,17]
Skeletal deformities and growth abnormalities	Limbs, forearm, joints	Progressive angular deformities (knee/ankle valgus), limb disproportion, short stature, bowing of forearm with ulnar shortening, and radial head subluxation; may restrict joint movement and predispose to early osteoarthritis.	[10,18]
Neurovascular involvement	Peripheral nerves, spinal canal	Compression by exostoses causing paresthesia, ischaemia, or rarely spinal cord compression and neurological deficits.	[4,19]
Scapular manifestations	Ventral scapula	Pseudo-winging of scapula, snapping during shoulder motion, and limited scapulothoracic movement; may cause visible deformity or asymmetry even without pain.	[20,21]
Chest wall and rib lesions	Ribs, intercostal nerves	Neuralgic pain due to involvement of ribs or intercostal nerve compression; occasionally associated with painful bursitis in large chest wall lesions.	[20,22]
Emerging manifestations	Mediastinum, thoracic cavity	Rare cases of visceral or mediastinal invasion by exostoses leading to compression of internal organs; reported example includes anterior mediastinal osteochondroma/chondrosarcoma compressing the right ventricle without typical thoracic symptoms.	[23]

[Table/Fig-2]: Classical and emerging clinical manifestations of Hereditary Multiple Exostoses (HME) [4,10,16-23].



[Table/Fig-3]: Schematic representation of the molecular pathway in Hereditary Multiple Exostoses (HME).
EXT1: Exostosin-1; EXT2: Exostosin-2; HS: Heparan sulfate; IHH: Indian hedgehog, FGF: Fibroblast growth factor; BMP: Bone morphogenetic protein

conditions typically lack germline EXT1/EXT2 mutations, and the risk of malignant transformation (~20–50%) is significantly higher than in HME (~2-5%) [2,29].

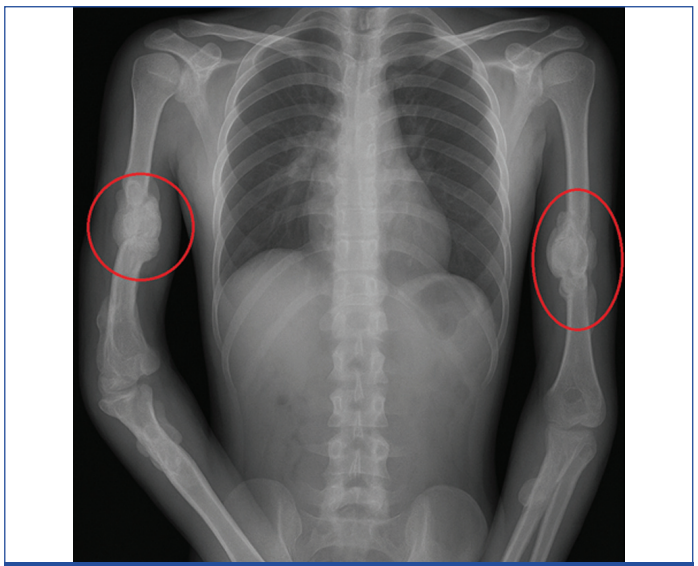
Other genetic syndromes, such as metachondromatosis, can feature both exostoses and enchondromas and are caused by pathogenic variants in PTPN11 (e.g., splice-site mutation in exon 11), rather than EXT1 or EXT2 [30]. Contiguous gene deletion disorders, such as Langer-Giedion syndrome (EXT1 + TRPS1 deletion) or Potocki-Shaffer syndrome (EXT2 + ALX4 deletion), should also be considered when non skeletal phenotypes such as craniofacial dysmorphism, intellectual disability, or parietal foramina are present [31].

In clinical genetics practice, when multiple osteochondromas are observed, molecular testing of EXT1/EXT2 confirms HME. In cases lacking these mutations or with atypical clinical or radiologic features, other genes may need to be investigated [13].

Radiologic and Molecular Diagnosis of Hereditary Multiple Exostoses (HME)

Clinical diagnosis of HME is primarily radiologic: the presence of two or more osteochondromas in juxta-epiphyseal bone sites is sufficient according to World Health Organisation (WHO) standards. Genetic testing for EXT gene mutations, which affect HS biosynthesis, is employed in cases of diagnostic uncertainty or when a family history is present [4,17].

Plain radiography (X-rays) remains the first-line modality for evaluating HME [32]. X-rays provide a clear depiction of osteochondromas as bony outgrowths in the metaphyses of long bones, demonstrating continuity between the cortex and medullary bone and the parent bone. They may also reveal characteristic skeletal deformities, such as bowing, shortening (e.g., ulnar foreshortening, Madelung-type deformity), diametaphyseal widening, and joint involvement [32,33]. Representative X-ray images of typical HME osteochondromas are shown in [Table/Fig-4]. Radiography is widely accessible, cost-effective, and relatively simple, making it suitable for imaging shoulders, pelvis, knees, and wrists in suspected HME cases [33]. However, X-rays have limitations: they poorly visualise the cartilage cap, soft-tissues, or complex bones (e.g., ribs, scapula), and cannot fully assess involvement of adjacent structures [33].



[Table/Fig-4]: Representative X-ray showing typical osteochondromas in a patient of Hereditary Multiple Exostoses (HME); Source- Authors.

For more detailed evaluation, particularly when complications or malignancy are suspected, MRI and CT are employed [34]. MRI

is the modality of choice for assessing soft-tissue, visualising surrounding muscles, vessels, and nerves, and identifying bursitis or oedema [17,34].

Advanced Imaging, Malignant Transformation, and Management in HME

CT, and multidetector CT (MDCT) in particular are useful in the definition of cortical and medullary continuity in complex anatomy (spine, pelvis, scapula), cortical cartilage caps, cortical destruction or irregularity, fracture, and preoperative planning [35]. Whole-body/total-body MRI (WB-MRI/TB-MRI) and new tools of high-metabolic imaging are evolving as the next step to enhance the earliest sign of complications in HME [29]. Large single-centre series and reviews demonstrate that TB-MRI has the capability of screening the entire skeleton in a single-session to sensitively identify cartilage-cap thickenings and peripheral chondrosarcomas, especially those of flat bones (ribs, scapula, pelvis), and thereby helps to filter out higher-risk patients to further work up [29,36].

Radiotracer methods such as FDG PET/CT and hybrid PET/MR serve as adjuncts in cases of suspected malignant transformation by providing objective metabolic data [37]. Integration of clinical and morphologic features should raise suspicion for chondrosarcoma [4]. Clinically, new-onset or worsening pain at the site of an osteochondroma—especially pain not associated with mechanical irritation or additional growth after skeletal maturity—is considered a red flag [4].

MRI findings suggestive of malignant transformation include: irregular or thickened cartilage cap (usually >1.5–2.0 cm), cortical breach, interruption of medullary continuity, soft-tissue mass, and heterogeneous signal or contrast enhancement [4,38]. When morphology is ambiguous, histologic evaluation remains the gold standard; however, high-grade foci may be missed due to sampling error in heterogeneous lesions. Therefore, integration of imaging, clinical history, and, where available, molecular findings is essential for accurate diagnosis and management [4,38].

Although there is no universally accepted numeric threshold for lesion growth or cartilage-cap thickness after skeletal maturity, the general clinical rule is: any increase in size or cap thickness in skeletally mature patients is suspicious and warrants close follow-up [38]. FDG PET/CT (and PET/MR when available) is particularly useful, as it provides objective metabolic information. SUVmax correlates with histologic grade: benign cartilaginous lesions have very low uptake, whereas higher-grade chondrosarcomas exhibit increased SUVmax [39]. Absolute SUV thresholds depend on the scanner, protocol, and lesion location, but significantly elevated or heterogeneous uptake is a strong indication for biopsy and more aggressive treatment [37,39]. PET/MR offers the additional advantage of superior soft-tissue characterisation, aiding in local staging and surgical planning [37].

Most conventional chondrosarcomas are resistant to standard chemotherapy and radiotherapy; therefore, surgical resection with adequate oncologic margins remains the primary treatment [38]. The surgical approach—wide resection versus intralesional curettage—is determined by tumour grade, location, and functional considerations. Low-grade, appendicular atypical cartilaginous tumours may be treated with intralesional surgery or active surveillance in select cases, whereas high-grade and central pelvic or axial tumours require wide resection [38,40]. Adjuvant radiotherapy is indicated in cases of positive margins, unresectable disease, or for palliation, while systemic chemotherapy is limited to high-grade or dedifferentiated histologies or clinical trials of targeted agents [38,40].

Histologic grade and stage are key determinants of prognosis. Low-grade lesions (grade 1/atypical cartilaginous tumours) generally have excellent local control and long-term outcomes. Intermediate- and high-grade chondrosarcomas have higher rates of local recurrence and metastasis, particularly to the lungs [41]. Reported 5-year overall survival varies by grade: grade 1 disease >85–90%, grade 2 disease ~70–75%, grade 3 disease 50–60% or less, with dedifferentiated chondrosarcomas carrying a poor prognosis [41]. Independent prognostic factors include margin status and the presence of metastases at diagnosis. These data underscore the importance of accurate grade assignment and early detection of malignant transformation [41].

Although there is no universally approved, evidence-based surveillance schedule for HME, consensus recommendations advocate risk-stratified surveillance [42]. High-risk lesions—those located in the pelvis or scapula, symptomatic, suspicious on imaging, or associated with family/genotype risk factors—should be followed more closely [42]. For pelvic and scapular lesions, cross-sectional imaging (MRI ± PET) every 2–3 years has been suggested, whereas for other lesions, clinical review and targeted imaging in response to new pain or growth is recommended [42]. In any adult presenting with new pain, growth after skeletal maturity, or suspicious MRI features, MRI evaluation and consideration of FDG PET/CT (or PET/MR) and early biopsy are strongly advised [42].

Similarly, radiomics and machine learning-based models applied to routine X-rays and MRI have shown very promising diagnostic accuracy in differentiating between benign osteochondromas and low- or high-grade malignant changes [43,44]. Specific NGS panels can detect point mutations and small indels in EXT1/EXT2, while genome sequencing and RNA studies can identify large duplications, structural variants, or mosaic events that might otherwise be missed, converting an otherwise "genetic-negative" diagnosis into a confirmed molecular diagnosis [45,46]. Diagnostic modalities and imaging advances in HME are summarised in [Table/Fig-5] [17,32-37,43-47].

Diagnostic modality	Key features and diagnostic role	Advantages	Limitations / remarks	References
Plain Radiography (X-ray)	Shows multiple osteochondromas at juxta-epiphyseal regions with continuity between cortex and medulla; identifies skeletal deformities such as bowing, ulnar shortening, and diametaphyseal widening.	Widely available, inexpensive, and effective for skeletal overview.	Poor visualisation of cartilage cap and soft-tissues; limited in complex bones (ribs, scapula, pelvis).	[32,33]
Computed Tomography (CT) / Multidetector CT (MDCT)	Defines cortical and medullary continuity in complex bones; useful for cortical destruction, irregularity, fractures, and preoperative planning.	Excellent bony detail; rapid acquisition.	Limited soft-tissue contrast; radiation exposure.	[35]
Magnetic Resonance Imaging (MRI)	Assesses cartilage cap thickness (<15–20 mm in adults), signal intensity (low–high on T1, high on T2/STIR), and enhancement with gadolinium; evaluates soft-tissue, bursitis, oedema, and neurovascular involvement.	Gold standard for soft-tissue characterisation; no ionising radiation.	Costly and time-consuming; not always available.	[17,34]
Ultrasound (USG)	Detects superficial cartilage caps and soft-tissue involvement.	Non invasive, quick, and inexpensive.	Operator-dependent; limited depth penetration.	[17,47]
Nuclear Imaging (Bone Scan, PET/CT)	Identifies metabolic activity of lesions; FDG PET/CT used for assessing possible malignant transformation (e.g., chondrosarcoma).	Provides metabolic information; useful adjunct to MRI.	Low specificity; radiation exposure.	[17,37,47]

Whole-Body / Total-Body MRI (WB-MRI/TB-MRI)	Enables single-session screening of entire skeleton for cartilage-cap thickening and peripheral chondrosarcoma, especially in flat bones (ribs, pelvis, scapula)	High sensitivity for early detection and risk stratification	High cost; limited accessibility in many centres.	[29,36]
Radiomics and Machine Learning Models	Analyse imaging data (X-ray, MRI) to differentiate benign vs. malignant lesions based on quantitative features	High diagnostic accuracy; non invasive	Still emerging; needs larger validation studies	[43,44]
Genetic Testing (EXT1/EXT2 Mutation Analysis)	Detects EXT gene family mutations affecting Heparan Sulfate (HS) biosynthesis; confirms diagnosis in uncertain or familial cases	Provides definitive molecular confirmation; aids genetic counseling	May miss large structural variants if not using advanced methods	[46]
Next-Generation Sequencing (NGS), Genome and RNA Studies	Identifies point mutations, indels, duplications, structural variants, and mosaic events missed by routine tests	Comprehensive mutation detection; improves "genetic-negative" cases	Requires specialised facilities; expensive	[45,46]

[Table/Fig-5]: Diagnostic modalities and imaging advances in Hereditary Multiple Exostoses (HME).

Genetic Counselling, Prenatal Diagnosis, and Family Screening in Hereditary Multiple Exostoses (HME)

HME requires preconception counselling so families can understand its autosomal-dominant inheritance, a recurrence risk of approximately 50%, and variable clinical expressivity [10]. Genetic counselling empowers couples to make informed reproductive decisions, including natural conception with prenatal testing or preimplantation genetic diagnosis when familial EXT1 or EXT2 mutations are present [10]. At-risk pregnancies can be identified prenatally through chorionic villus sampling or amniocentesis [48]. Affected families should receive periodic clinical and radiographic assessments to detect further deformities and complications [49]. Whole-body imaging is generally not required in the absence of symptoms or high-risk factors [49]. Genetic testing of asymptomatic family members should only be performed if a pathogenic mutation has been identified in the family and should include counseling to discuss medical, ethical, and psychosocial implications, particularly in children, as the results may affect care [4,12].

Conventional Treatment and Operative Strategies in HME

Treatment of HME is primarily symptomatic and surgical. In asymptomatic cases, lesions are typically detected during routine clinical examination and radiographic follow-up [50]. Surgical excision is indicated for symptomatic osteochondromas, rapidly growing lesions, or lesions causing cosmetic defects or functional impairment [50]. Excision involves removal of the cartilage cap and perichondrium to reduce recurrence. In children, resections of single lesions are common, but surgeons are cautious about removing lesions involving the physis due to potential effects on growth [51]. Deep or complex sites, such as the hip, pelvis, or spine, require multidisciplinary planning [51,52].

For deformities or limb-length discrepancies (e.g., forearm deformities, genu/ankle valgus, hip coxa valga), orthopaedic corrective procedures may include osteochondroma excision with corrective osteotomy, ulnar lengthening, radial osteotomy, guided growth (haemiepiphysiodesis), epiphysiodesis, or limb-lengthening procedures [17,53,54]. Recent series report good outcomes with guided growth in preventing progressive hip and knee deformities in growing children, and specialised approaches such as Ganz surgical dislocation have been applied in difficult femoral-neck lesions [55,56]. Conventional and surgical management of HME is summarised in [Table/Fig-6] [17,50,56].

Emerging and Disease-Modifying Therapies in Hereditary Multiple Exostoses (HME)

Recent research has identified molecular therapeutic candidates aimed at altering disease pathogenesis rather than just providing symptomatic relief. Among the most promising is palovarotene, a selective retinoic acid receptor gamma agonist. In mouse models with EXT1/EXT2 deletion, palovarotene decreased osteochondroma formation by up to 91% when administered early, and it appeared to suppress dysregulated BMP signaling and abnormal fate decisions by perichondrial progenitor cells [57]. Another potential therapeutic approach involves heparanase inhibition (e.g., SST0001), which has been shown to reduce unregulated chondrogenesis by altering the accessibility of HS and its downstream effects on BMP and other signaling pathways [4,58]. These therapies are in preclinical or early clinical trials, representing a shift toward disease-modifying strategies [4,57].

Impact on Functional Ability, Psychosocial Wellbeing, and Quality of Life in HME

HME can significantly impair daily functioning in children and adolescents by causing pain, limited range of motion, and joint

Category	Indications	Procedures / approaches	Advantages	Limitations / considerations	References
Conservative (non operative)	Asymptomatic lesions; incidental findings on follow-up	Regular clinical examination and periodic radiographic surveillance	Non invasive; avoids unnecessary surgery; early detection of progression or malignant transformation	Does not correct deformities; requires long-term monitoring; risk of delayed intervention if lesion becomes symptomatic	[50]
Surgical excision	Symptomatic lesions (pain, deformity, functional/cosmetic impairment); rapidly growing masses	Complete excision of osteochondroma including cartilage cap and perichondrium	Relieves pain; restores function; reduces recurrence risk	Risk of recurrence if excision is incomplete; growth disturbance if near physis; surgical complications	[50,51]
Multidisciplinary planning	Deep or complex lesions (hip, pelvis, spine)	Collaborative planning among orthopaedic, neurosurgical, and radiologic teams	Ensures safe resection; minimises complications; optimises functional outcomes	Requires coordination among specialists; resource-intensive	[51,52]
Corrective orthopaedic procedures	Limb deformities or discrepancies (forearm deformity, genu/ankle valgus, hip coxa valga, limb-length inequality)	Osteochondroma excision with corrective osteotomy; ulnar lengthening or radial osteotomy; guided growth (haemiepiphysiodesis); epiphysiodesis; limb lengthening	Corrects deformities; improves limb function and alignment; can prevent future complications	Technically demanding; staged procedures may be required; potential for growth disturbance	[17,53,54]
Advanced techniques	Complex femoral-neck or periarticular lesions	Specialised approaches such as Ganz surgical dislocation	Full access for complete excision; preserves vascular supply; good postoperative function	High surgical expertise required; risk of complications; limited availability	[55,56]

[Table/Fig-6]: Conventional and surgical management of Hereditary Multiple Exostoses (HME) [17,50-56].

deformities, which restrict participation in sports and recreational activities [59]. These physical limitations often translate into psychosocial burdens, including lower self-esteem, social withdrawal, and body image concerns, particularly in teenagers with visible lumps or gait differences [59,60].

Later school and occupational outcomes may include absenteeism from activity-related limitations, restricted physical education, and challenges in manual jobs requiring full mobility. Adolescents may also face transitional care and self-management issues, further impacting educational and vocational performance [60]. Quality of life in HME has been assessed using generic and musculoskeletal-specific instruments (e.g., SF-36/SF-12, CHQ-PF50, GHQ-12) and disease-oriented tools such as the Paediatric Outcomes Data Collection Instrument (PODCI) and pain scales (VAS), which evaluate physical functioning, pain, social functioning, and psychosocial well-being [61].

Future Research Directions in HME

Future studies should focus on three key areas:

1. **Genetics:** Identifying novel loci or intronic/structural variants in EXT1/EXT2-negative cases [51,62].
2. **Pathophysiology:** Clarifying the role of HS deficiency in disrupting growth-plate signaling pathways (e.g., BMP, FGF, Hedgehog) that trigger osteochondroma initiation and progression, enabling pathway-targeted interventions [51,62].
3. **Therapeutics and biomarkers:** Developing and clinically validating disease-modifying therapies (e.g., palovarotene, heparanase inhibitors) to inhibit exostosis formation, growth, or malignant transformation, and incorporating advanced imaging, radiomics, and longitudinal biomarkers to detect early malignant degeneration [62].

This narrative review updates current understanding of genetic factors, newer imaging technologies, and novel management approaches in HME, with a focus on translational and future research opportunities.

CONCLUSION(S)

HME is a rare autosomal-dominant bone disorder characterised by multiple cartilage-capped bony projections that can cause pain, deformity, functional impairment, and, rarely, malignant transformation. Imaging modalities such as MRI, CT, and novel whole-body technologies, combined with genetic testing, allow accurate diagnosis and early risk stratification. Management is primarily symptomatic and includes surveillance, surgical excision, and corrective orthopaedic interventions. Emerging molecular therapies, including palovarotene and heparanase inhibitors, have the potential to modify the disease course and improve patient outcomes.

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PARTICULARS OF CONTRIBUTORS:
1. Junior Resident, Department of Orthopaedics, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
2. Professor and Head, Department of Orthopaedics, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
3. Junior Resident, Department of Orthopaedics, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
4. Junior Resident, Department of Orthopaedics, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
5. Undergraduate Student, Department of Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Shashank Yadav,
Junior Resident, Department of Orthopaedics, Jawaharlal Nehru Medical College,
Datta Meghe Institute of Higher Education and Research,
Wardha-442107, Maharashtra, India.
E-mail: shashankyadav0029@gmail.com

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