

Surgical Operations and Consideration in Patients with Multiple Hereditary Exostoses: A Single Center Retrospective Study

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ABSTRACT

KEYWORDS

Multiple Hereditary Exostoses (MHE), Surgical Treatment, Pediatric Orthopedics, Bone Tumor.

Multiple Hereditary Exostoses (MHE) is a rare autosomal dominant skeletal disorder characterized by the formation of multiple osteochondromas that may lead to deformities, functional impairment, and potential malignant transformation. Despite advances in understanding its genetic basis, optimal surgical management remains a clinical challenge, particularly in developing countries where delayed diagnosis is common. This study aims to evaluate the profile of MHE patients and analyze the surgical treatments performed at a single orthopedic center. A retrospective descriptive and analytical study was conducted at Soeharso Orthopedic Hospital between 2021 and 2024. A total of 67 patients diagnosed with MHE who underwent surgical intervention were included. Data were analyzed using Microsoft Excel and SPSS, focusing on demographic characteristics, bone involvement, and types of surgical procedures. The results showed that the majority of patients were aged 11–15 years (44%) and predominantly male (59.7%). The most commonly affected bones were the radius-ulna (31%) and tibia-fibula (28%). A total of 88 surgical procedures were performed, with biopsy (46.6%) and excision (19.3%) being the most frequent interventions. These findings highlight the importance of biopsy for definitive diagnosis and complete excision to prevent recurrence. In conclusion, surgical management plays a crucial role in improving patient outcomes and quality of life in MHE. Early diagnosis and appropriate intervention strategies are essential to minimize complications and optimize long-term prognosis.

INTRODUCTION

An inherited genetic skeletal condition of the enchondral bone is called Multiple Hereditary Exostoses (MHE). Multiple exostoses are a feature of this autosomal dominant condition that affects the juxtaepiphyseal area of the long bones (Mishra et al., 2019a). A point mutation of MHE is in the exostosin (EXT) family of genes, also referred to as tumor suppressor genes. While the medical approach to treating MHE is still developing, surgery is the primary therapeutic method (Goud et al., 2012).

Compared to solitary exostosis, the condition occurs in only 5% to 10% of instances, is more common in boys (1.5:1), and is typically identified before the patient reaches the age of 10 (D'Arienzo et al., 2019). 12% of osteochondroma who can be developed in MHE (Sasaki et al., 2022). Since many individuals with asymptomatic lesions have never received a diagnosis, the true frequency of MHE is unclear; therefore, the estimated prevalence in the Western population is between 1: 50,000 to 1: 100,000. It was once believed to be male dominance, but HME now seems to have an equal impact on both sexes (Ayu & Iqbal, 2023). With the exception of the facial bones, osteochondromas can develop from any segment. Any bone that develops from endochondral ossification may be affected by the illness. The metadiaphyseal segments of long bones are the most afflicted, even though exostosis originates more commonly in the scapulae, ribs, pelvis, and vertebrae. There have been no reports of tarsal, carpal, or cranial involvement (Hamdi et al., 2022; Pedrini et al., 2011).

Surgery is only required in cases with symptoms in order to prevent complications later on. Procedures like limb length equalization, osteotomy-assisted deformity repair, and epiphysiodesis are commonly considered. Many opinions on how to treat these deformities were presented in recent literature. Some suggested vigorous early surgical intervention to stop or slow the progression of abnormalities and or functional impairment.

Literature Review

Multiple Hereditary Exostoses (MHE)

Multiple hereditary exostosis (MHE) is a genetic disorder that causes multiple osteochondromas, developing a number of benign osseocartilaginous lesions, most frequently in the near of the long bones metaphyseal areas. A point mutation in the exostosin (EXT) gene family, also referred to as tumor suppressor genes, causes MHE, an autosomal dominant disorder. This autosomal dominant illness has also been named hereditary multiple osteochondromas, hereditary deforming dyschondroplasia, diaphyseal aclasis and multiple cartilaginous exostoses.

1. Epidemiology

An uncommon genetic condition known as multiple hereditary exostoses (MHE) causes a number of incidence 1:50,000 in western nations. It nearly completely happens in males. The condition can be inherited directly from an affected parent, typically the father, in over 50% of patients. Compared to isolated exostosis, the condition occurs in only 5% to 10% of instances, is more common in boys (1.5:1), and is typically detected before the patient turns 10. 80% of patients receive a diagnosis by the age of ten, with a mean diagnostic age of 3 years. With the exception of the facial bones, osteochondromas can develop from any segment. Any bone that develops from endochondral ossification may be affected by the illness. The metadiaphyseal segments of long bones are the most afflicted, even though exostosis originates more commonly in the scapulae, ribs, pelvis, and vertebrae. There have been no reports of involvement of the tarsal, carpal, or cranial bones. According to reports, 0.5% to 25% of individuals develop malignant degeneration to chondrosarcoma, and an EXT1 mutation increases the chance of severe clinical symptoms.

Etiology and Pathogenesis

MHE primary cause is exostosin-1 (EXT1) and exostosin-2 (EXT2), a monogenetic autosomal dominant condition. Chromosome 8 as an EXT1 gene that was discovered at locus 8q24.1. The EXT2 gene was discovered at locus 11p11–13 on chromosome 11. Between 70 and 94 percent of human patients had these mutations, with EXT1 having a higher frequency. Additionally, patients with mutations in the EXT1 gene are more likely to have more pelvic involvement, limb malalignment, exostoses, and shorter stature (Beltrami et al., 2016; Roach et al., 2009).

Mechanisms of MHE involved heparan sulfate (HS) polymerase inactivation agents, post-translational EXT-products/inhibitors, and miRNAs as epigenetic factors that may prevent EXT-translation. The HS molecule is closely associated with the molecular process that results in the production of exostosis and MHE. Over the years, a number of studies have claimed that EXT mutations cause the HS chains to not elongate sufficiently. The Golgi reticulum-based complex formed by the products of the EXT1 and EXT2 genes is crucial for the synthesis and function of the glycosyltransferase enzyme, which is ultimately in charge of the chain polymerization of HS. This explains why disease can be caused by

solitary mutations of EXT1 or EXT2; in fact, the Golgi complex cannot function properly without the components of EXT1 or EXT2.

The extracellular matrix uses the HS chains for a variety of purposes. It is thought that significant diversity in chondrocyte differentiation or proliferation pathways may result from the presence of shorter HS chains or from their absence. The diffusion of Indian hedgehog (IHH) in the development plate may be mediated by extracellular HS chains. IHH is a crucial component that controls chondrocyte development and differentiation. The distribution, range of action, stability, and target action of a number of other factors, including bone morphogenetic proteins (BMPs), fibroblastic growth factors (FGFs), the Wnt signaling pathway (Wnts), and parathyroid hormone-related proteins (PTHrPs), are likewise influenced by HS chains.

Osteochondromas and other MHE symptoms, such as low height, are caused by a significant disruption to these signaling pathways. An imbalance in the extracellular matrix of signals and substances that promote chondrocyte differentiation or proliferation is the cause of osteochondromas. Autistic mice with normal brain morphology have also been shown to have impaired HS chains, and it has been proposed that HS chains play a role in the integrity of glutamatergic synapses.

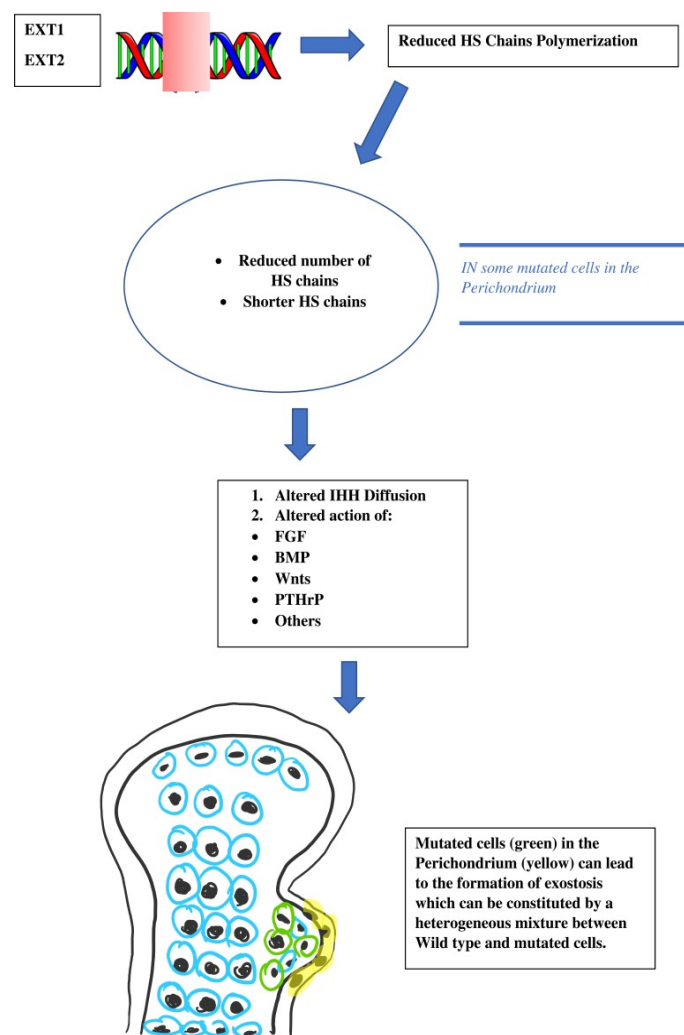


Figure 1. Pathogenesis MHE.

2. Macroscopy and Microscopy Pathology Anatomy

Macroscopic findings of MHE are surrounded by a periosteum layer. A distinct bony stalk with a cartilage crown is present Fig. 2A. The stalk might be wide or thin and pedunculated. The cartilage cap's thickness increases with age, with younger individuals having a thicker cap. Microscopic MHE showed a periosteum covering the cartilage cap. Clusters and lacunae are the chondrocytes seen in the cap's surface portion. Those facing the base form a line that resembles a growth plate. Enchondral ossification is frequently observed below this (Fig. 2B). In osteochondromas that are actively forming, the cartilage cap may occasionally contain binucleate chondrocytes (Miraj & Asdi, 2018; Mishra et al., 2019b).

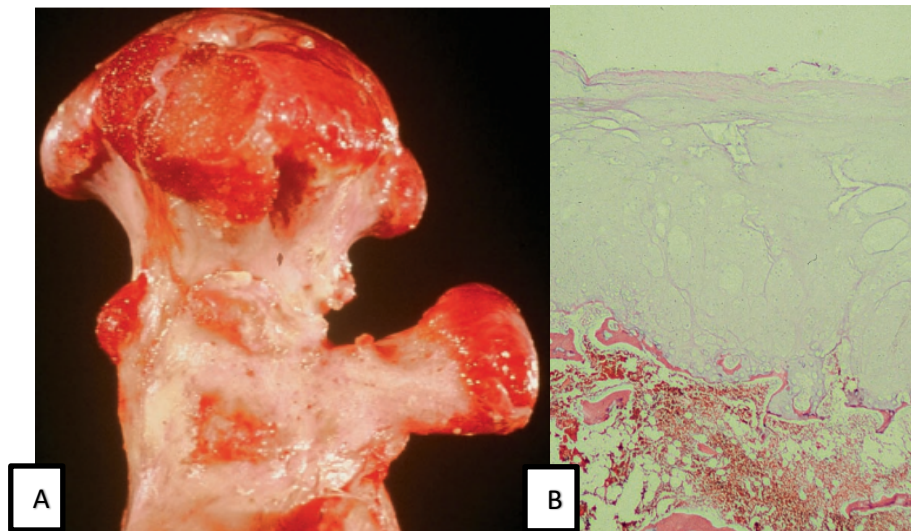


Figure 2. Macroscopic of MHE (A) and microscopic findings showed a thin cartilage cap surrounded by perichondrium is seen on the surface of an osteochondroma. The cartilage has only a minor myxoid alteration. Endochondral ossification is taking place where the marrow and underlying bone meet. (B).

3. History and Physical Examination

Early onset osteochondromas typically have larger lesions that grow in line with the growth plate and adjust to the diaphysis's evolution, causing disturbances in the growing diaphysis and characteristic deformations that typically affect the distal femur, radius, ankle, and ulna, as well as the ribs and proximal tibia, where exostoses are palpable and easily visible. MHE patients may have a coxa valga at the hip joint, while the knee joint is typically affected, with genu valgum being the most common deformity that affects about one-third of MHE patients (Hams et al., 2020; Masino et al., 2024).

Spinal exostoses can cause severe and acute neurological syndromes. Patients with MHE are typically shorter, especially those with EXT1 mutations, and many are also diagnosed with nerve entrapment syndromes, reduced range of motion or paresthesia, and chronic inflammatory syndromes (Fei et al., 2019).

4. Evaluation

Radiographs can typically focus osteochondromas in the appendicular skeleton; computerized tomography can be considered for regions that are difficult to visualize (thorax, spine, pelvis); magnetic resonance imaging (MRI) allows for accurate measurement of cartilage cap thickness and the effect of the lesion on surrounding soft tissue structures;

and it clearly shows continuity of the cortex and medulla from the osteochondroma to the parent bone. However, since the majority of patients are asymptomatic at birth, genetic screening is the only way to make an early diagnosis, such as with registered affected families (Sato et al., 2020).

5. Surgical Treatment

Palovarotene (PVO) is a selective retinoic acid receptor gamma agonist that has been studied as a potential target treatment for fibrodysplasia ossificans progressiva (FOP) could decrease formation of exostosis in mice with EXT1-EXT2 deletion. Surgical excision was performed by removing the exostosis at the base of the bone, which resulted in the removal of the cartilage cap. Usually, when the cartilage cap is removed completely, there are no recurrences; however, complete removal in some regions may be needed for reconstruction techniques such as internal fixations and bone grafting. Recurrences may occur when wide excision is not feasible, and surgery is required in cases with moderate to severe limb length discrepancies, severe limb malalignment, or segment shortenings (Bukowska-Olech et al., 2021; Jarvis & Khurana, 2014). In order to treat deformity in MHE, lengthening bone, example the ulna and correcting the radius—especially with the aid of an external fixator—produced predictable results. Techniques for correcting the genu valgus and wrist abnormalities linked to MHE throughout the growing period have been proposed for the knee and radius stapling. With the best outcomes, fibular lengthening has also been tested in the prevention and early treatment of talus instability and ankle valgus deformities. We advise surgically excising the lesion when a symptomatic exostosis is found in cases of neurovascular structure entrapments or damages. Technique wedge osteotomy could correct deformity like genu valgum like Mishra et al used wedge osteotomy in patient with neck and greater trochanter of femur.

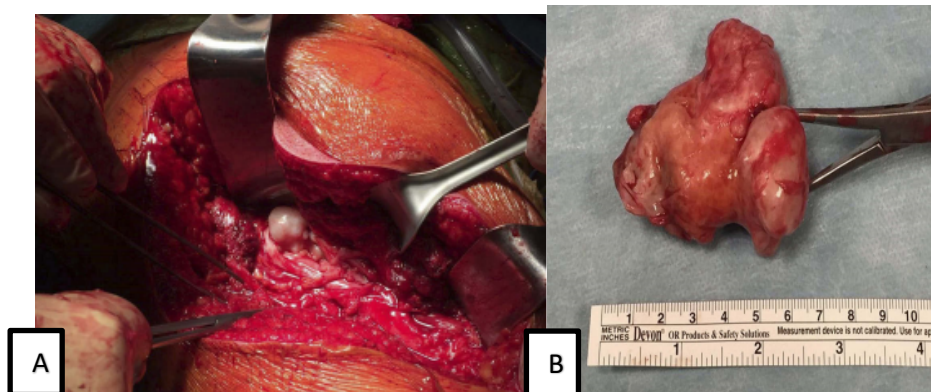


Figure 3. Intraoperative surgical excision (A) and resected specimen (B) .



Figure 4. Osteotomy for radial bending correction and ulnar lengthening sequences that transform the Ilizarov frame into an internal fixing.



Figure 5. A case with left knee and genu valgum had severe flexion movement restrictions (a). Excision and corrective osteotomy were used to manage him (b).

6. Differential Diagnosis

Enchondromas might be mistaken for rarely exostoses. The origin of enchondromas differs from that of MHE since they are benign, typically asymptomatic intra-osseous tumors of hyaline cartilage caused by somatic mosaic mutations of the IDH1 and IDH2 genes. Another condition that resembles MHE in clinical presentation is metachondromatosis, which is characterized by numerous enchondromas and exostoses. Exostoses are also present in Langer-Giedion syndrome, a condition characterized by short stature, intellectual impairment, and characteristic facial dysmorphism, among other clinical signs. Another differential diagnosis for the most prevalent type of dwarfism is achondroplasia, in which patients exhibit classic small height, disproportionate limb shortening, and metaphyseal abnormalities without exostoses (Pacifci, 2019).

7. Prognosis

As a chronic condition, MHE necessitates close monitoring to prevent numerous potential consequences. Periodic screening should be performed on children every 6 to 12 months since crucial areas like the spine need to be monitored and some growth disorders can be corrected early with very easy procedures. To prevent neurological damage, Roach et al. advise children with MHE to get a full columnar MRI every two years to detect intraspinal exostoses and possible intramedullary affection.

It is advised that adult patients have routine clinical examinations every 12 to 24 months, depending on the key risk areas (proximal femur, scapula, and pelvis), in order to detect malignant transformation early and treat it appropriately. However, because secondary chondrosarcomas rarely spread, the prognosis is favorable; the projected 5-year survival rate is 90%.

8. Complications

The malignant transformation of an existing osteochondroma into a secondary peripheral chondrosarcoma during adulthood is a complication of MHE. Costal exostoses are generally asymptomatic, but they can infrequently result in intra-thoracic complications, such as hemothorax, pneumothorax, and damage to the pleura, lung, diaphragm, or pericardium. The abnormal pelvic morphology or the presence of osteochondromas on the inside of the pelvis can cause complications during delivery. Motion impairments, skeletal

deformations, persistent pain, growth retardation, and the potential for malignant development of exostoses can all significantly impact a patient's quality of life.

METHOD

Research Setting

A single center retrospective, descriptive, and analytical study was conducted at Soeharso Orthopedic Hospital over a four-year period from 2021 to 2024

Research Design

The study employed a retrospective design to analyse and describe the data collected during the specified period. The study utilized Microsoft Excel 2010 and SPSS for data analysis to assess treatment options in MHE.

Sampling

1. Inclusion Criteria
 - a. Patients who were diagnosed with MHE in Soeharso Orthopedic Hospital over a four year period from 2021-2024
 - b. Patient underwent surgery in Soeharso Orthopedic Hospital.
2. Exclusion Criteria
 - a. Patients with abnormalities not brought on by MHE.
 - b. Patients who had already undergone surgery at another facility were excluded.
3. Treatment Surgical Options

We evaluated surgical treatment for every patient that consists of osteoarthrotomy, biopsy, condylectomy, reduction dislocation, wedge osteotomy, external fixation, limb lengthening, excision, reconstruction. We also evaluated the location of every part of bodies who are affected by MHE.

Variable

The variables studied included socio-demographic factors such as age, gender, bone location, and treatment that had been done.

RESULT AND DISCUSSION

In periods 2021 – 2024 some patients had multiple hereditary exostoses (MHE) in Soeharso Orthopedic Hospital and the total was 67 with MHE. Period that has high patients with MHE was in 2024 with 24 patients. Age profile group that had high populations were 11-15 years (44%), followed with 6-10 years (28%) and with least patients were >25 years (3%) (Figure 8). Table 1 showed that male (59,7%) are more common in MHE than female (40,3%).

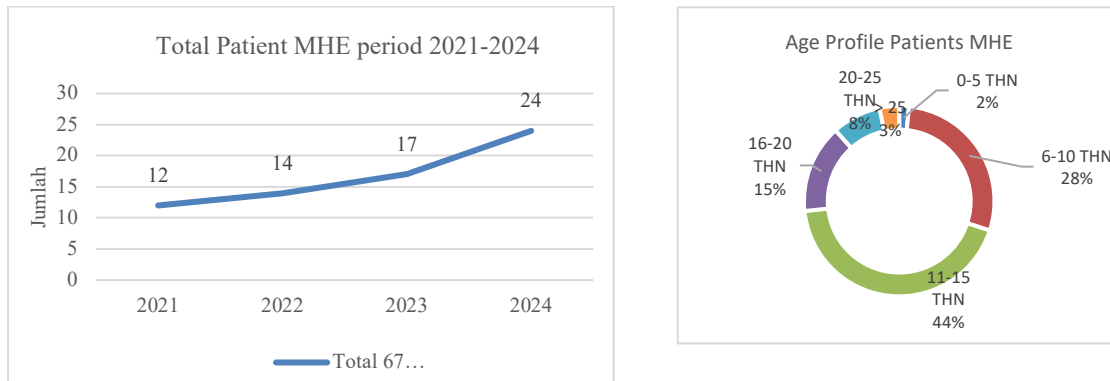


Figure 8. Total patient and age group distribution of MHE period 2021-2024.

Table 1. Distribution gender in MHE patients

Gender	Frequency	Percentage (%)
Male	40	59,7
Female	27	40,3
Total	67	100.0

Diagram 1 showed MHE data profile according to bone location. Location with the highest profile is radius, ulna (31%) followed by tibia fibula (28%). Location that has the least profile is shoulder, pelvic, tarsal metatarsal, and patella.

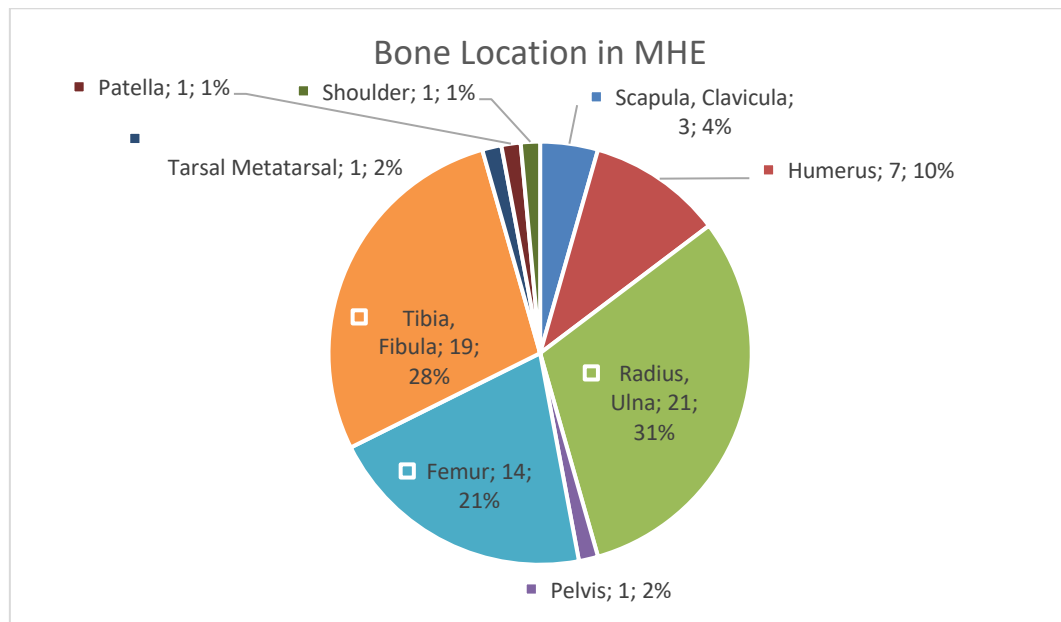


Diagram 1. Total profile MHE according bone location.

Table 2. Distribution of surgery treatment of MHE

Surgical Options	Frequency	Percentage (%)
Biopsy	41	46.6
Condylectomy	6	6.8
Reduction Dislocation	1	1.1
Excision	17	19.3
Osteotomy	1	1.1
Osteoarthrotomy	5	5.7
Wedge Osteotomy	1	1.1
Limb Lengthening	3	3.4
Bone Graft	1	1.1
External Fixation	8	9.1
Reconstruction	4	4.5
Total	88	100.0

Table 2. showed 88 total surgery treatments for 67 patients, so the patient could have multiple surgery therapy. Biopsy (46,6%) has the highest percentage surgical options for MHE, followed by excision on the lesion (19,3%) and for the least percentage was reduction dislocation (1,1%), wedge osteotomy (1,1%), and bone graft (1,1%).

In this study, 67 patients with MHE were identified. The most common age range was 11-15 years. These results are various in other countries. Case study in Japan showed that a patient with knee arthroplasty caused by MHE has been diagnosed at the age of 12 years. Cohort study that was held in Netherlands showed that media age patients with MHE are 29 years old with the range age being 1-80 years. In western population, MHE was diagnosed at 3 years old and 80% of patients were diagnosed by the age of 10 years. However, as certain patients are frequently observed pursuing traditional medicine before receiving medical attention, it is possible that patients in underdeveloped nations like Indonesia will arrive at the center late.

Our study found that MHE affected male patients more than the female patients. These results were in line with other studies. In Pedrini et al showed that male patients (50,7%) were more common than female patients (49,3%). Males appeared to have a higher prevalence of MHE in earlier research, but more current investigations have not discovered any indication of sexual predominance.

In this study, the most common bone locations in MHE patients are in radius ulna (21,31%) and tibia fibula (19,28%). A few studies showed the proximal tibia (84%), fibula (76%), humerus (72%), and distal femur (90%), are the bones most frequently affected. Osteochondromas are frequently initially found on the proximal tibia and ribs, where they are palpable and easily apparent. Since they form by intramembranous ossification, they are infrequently found in the tarsal and carpal bones and never in the face bones.^[5] Study in Saudi Arabia showed that radius and ulna could be common bone location of MHE with radius were 50% and ulna were 20%. Few studies showed The prevalence of forearm deformity in MHE patients ranges from 40% to 74%. Exostosis at the distal ulna results in a more severe forearm

deformity than exostosis at the radius because the ulnar bone has a smaller diameter and contributes more to longitudinal growth.

Biopsy and excision are the most surgical options in our study. Growth beyond skeletal maturity is one of the symptoms of these tumors, which form in the cartilage cap of an existing osteochondroma. However, a biopsy is necessary for a definitive diagnosis. Osteochondroma excision is typically a simple procedure, but in some specific places (such as the proximal femur), it can be extremely difficult, particularly if the lesion has a complex geometry that includes nerves or vessels. Surgical excision was performed by removing the exostosis at the bone base, which led to the removal of the cartilage cap. Recurrences are generally not possible when the cartilage cap is completely removed, but in some areas, complete removal may necessitate the use of reconstruction techniques like internal fixations and bone grafting.

Excision, which involves resection at the base of the exostoses, is a reasonably simple treatment with minimal morbidity. Internal fixation and allografting are two reconstructive methods that may be necessary for the biggest lesions. The development of a new lesion at the same area, particularly in very young children with open physis, or inadequate excision (it is crucial to remove the entire cartilage cap and the surrounding perichondrium to minimize the risk) may result in local recurrence. More involved surgeries including osteotomies, bone lengthening, and epiphysiodesis (in children) are frequently required to rectify malformations, misalignment, and limb length discrepancy.

CONCLUSION

This study aimed to MHE cases at Soeharso Orthopedic Hospital and evaluated surgery treatment to treat this case. There are 67 patients MHE that have undergone surgery. The majority cases were 11-15 years-old group with the most common bone location on upper extremity like radius and ulna (31%) and lower extremity like tibia and fibula (28%), and femur (21%) with biopsy (46,6%) followed by excision on the lesion (19,3%) was surgical options that the most held. Despite all of the surgical options, biopsy is necessary to get the definitive diagnosis and by removing all of the tumors was the main choice to inhibit recurrence of the MHE. A patient's quality of life may be greatly impacted by skeletal abnormalities, chronic pain, motion impairments, and the possibility of exostosis developing malignantly, therefore surgical options may help to increase patients quality of life depending on every case and situation of MHE.

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