

# The MHE Research Foundation



Wings of HOPE as we REACH for the  
CURE to Multiple Hereditary Exostoses

**The Connection Corner Guide to MHE / MO / HME**  
**Multiple Hereditary Exostoses**  
**Multiple Osteochondroma**  
**Hereditary Multiple Exostoses**



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## Dedication

The Connection Corner Guide book is dedicated to all people affected by MHE / MO / HME around the world. No family should need to face this disease and all the challenges that come along with it alone. No Physician should need to sit face to face with a family and not have the opportunity to provide a family the supportive information they require. The MHE Research Foundation would like to thank all the professionals who contributed their time, effort and energy that made it possible for this guide to be written.

Sincerely

The Board of Directors of the MHE Research Foundation

**The MHE Research Foundation is a nonprofit 501(c)(3) organization for the support of researchers, families and physicians dealing with (MHE) Multiple Hereditary Exostoses (MO) Multiple Osteochondroma a rare genetic bone disease. The MHE Research Foundation five point mission is to **REACH**, Advance & support the following.**

**RESEARCH**, to help researchers one day find a treatment / cure for MHE. Our foundation works hand in hand with researchers from around the world on this mission.

**EDUCATION**, to provide clinical information, guides to help benefit both families and physicians.

**ADVOCACY**, bring awareness about this disease throughout the world.

**CLINICAL**, to help provide resources to families enabling them to find the medical care they need.

**HOPE**, the research being conducted on MHE & the informational resources will bring a better quality of life to the families affected by this disease.

## Pure White Wings

All children are born as pure as small white doves with spirits eager to soar. With nurture and care, over time they spread their wings as they grow. With the warm summer breeze, parents take great joy in watching our kids learn to fly.

Flying around the clear blue sky with endless amounts of energy. Darting gracefully between cotton cloud dreams as these little doves fly after one another while playing and chasing their dreams.

You see our pure white doves were born with the same eager spirit, but also with BROKEN WINGS. Wings that are lame, bumpy and crooked, this hampers their ability to fly. Many times they simply watch through a window as others fly to follow their dreams. They can only imagine the feeling of boundless energies of freedom. Imagining what it would be like to dart at will between cotton cloud dreams, during the warm summer breeze.

While their wings maybe broken, their SPIRITS SOAR, giving these kids the unmatched strength, courage and determination to overcome and wisdom far beyond their years. It is their SPIRIT! Gracing them to find other adventures in life and spotting joy that others over look or take for granted.

Their energies are saved for times when it's needed for them to be able to overcome the challenges they face day in and day out. Their strength is used to endure the many surgeries and pain they face, trying to repair broken wings. Hoping that this surgery will be their last.

The WINGS OF HOPE lead the way as we REACH for the CURE!  
In order to fix our children's broken wings once and for all. To put an end to a life time of sitting on the side lines, watching others through the window. So they may also one day truly feel all the scenes of freedom others enjoy.

WHO ARE THESE WINGS OF HOPE? YOU ASK !!

THEY ARE EVERYONE OF US!!!

For you see, we are the care takers of the future, so others may one day be able to fly amongst clear warm blue skies of cotton cloud dreams.

Just the way life should be.

The **MHE / MO / HME Research and Education** being conducted today around the world, will open the WINDOW in the future and allow our children not only to FLY LIKE THE PURE WHITE DOVES THEY ARE, BUT SOAR LIKE EAGLES!!!!

**What is MHE / MO / HME ?**  
**Multiple Hereditary Exostoses (MHE)**  
**Often referred to as**  
**Hereditary Multiple Exostoses (HME)**  
**Multiple Osteochondroma**  
**is the preferred term used by the**  
**World Health Organization "WHO"**  
**Authored by the MHE Research Foundation**

MHE / MO / HME is a genetic bone disorder in which benign cartilage-capped bone tumors grow outward from the metaphyses of long bones, growth plates or from the surface of flat bones throughout the body. The severity of this disease varies widely. Some patients may have as few as two tumors, but most patients develop many more and the numbers of tumors can run into the hundreds.

These cartilage-capped bone tumors are called Exostoses / Osteochondroma and may be sessile or pedunculated and vary widely in size and shape.

Pedunculated Exostoses / Osteochondroma is when a stalk is present, the structure is called pedunculated. These have a Broccoli like appearance with stalk and growth towards the end of the stalk.

Sessile Exostoses / Osteochondroma have a broad-base attachment to the outer bone, called the "cortex". These have a lumpy / bumpy appearance (When no stalk is present, these are called sessile)

These Exostoses / Osteochondromas can cause numerous problems, including: compression of peripheral nerves or blood vessels; irritation of tendons and muscles resulting in pain and loss of motion; skeletal deformity; short stature; limb length discrepancy; chronic pain and fatigue; mobility issues; early onset arthritis; and an increased risk of developing malignant tumor transformation (chondro-sarcoma) reported risk of 2%-5% over life time. It is not uncommon for MHE / MO / HME patients to undergo numerous surgical procedures throughout their lives to remove painful or deforming Exostoses / Osteochondromas and or to correct limb length discrepancies and improve range of motion.

Surgery, physical therapy and pain management are currently the only options available to MHE / MO / HME patients, but their success varies from patient to patient and many struggle with chronic pain, fatigue and mobility problems throughout their lives.

MHE / MO / HME is a genetic autosomal dominant hereditary disorder. This means that a patient with MHE / MO / HME has a 50% chance of transmitting this disorder to his / her children. Approximately 10% -20% of individuals with MHE / MO / HME have the condition as a result of a spontaneous mutation are thus the first person in their family to be affected.

There are two known genes found to cause MHE / MO / HME they are EXT1 located on chromosome 8q23-q24 and EXT2 located on chromosome 11p11-p12. Approximately 60 to 70 %are located EXT1 gene and 20 to 30% are located EXT2 mutation. In 10 to 20% of the patients, no mutation is found.

# MHE / MO / HME Standards of Care Guide













There is an accompanying video presentation on the  
MHE Research Foundation website

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## Diagnostic Tools

### Important features of orthopedic exam:

It is important to follow each step of the exam during every office assessment of MHE

- |   |  |
|---|--|
|    | Patient should be comfortable with adequate exposure and well-lit surroundings (lest some important physical finding is missed.)   |
|    | It is important to assess how the patient moves about in the room before and during the examination as well as during various maneuvers. Balance, posture and gait pattern should also be checked.   |
|    | General exam findings should look for any lumps and bumps that can be felt on any anatomical sites that can be easily palpated. Chest wall, abdominal and deep pelvic exam should be performed in all cases. Sessile or pedunculated nature of the bumps should be ascertained if possible.  |
|    | General body habitus, including developmental milestones should be noted.  |
|  | It is important to note any obvious spinal asymmetry, deformities, trunk decompensation, and evidence of para-spinal muscle spasm or elevation suggestive of spinal lesions.   |
|  | The patient's height should be measured and monitored on subsequent visits. Individuals with MHE are frequently of short stature, with most having heights 0.5 to 1.0 SD below the mean. (The lesions tend to enlarge while the physes are open proportionate to the overall growth of the patient, and the growth of the osteochondroma usually ceases at skeletal maturity). |
|  | It is essential to perform and document a thorough neurologic exam. Asymmetric abdominal reflex is a subtle sign of spinal pathology and may be associated with spinal cord compression. Motor, sensory and reflex testing should be performed and recorded.   |
|  | Any discrepancies in limb lengths should be noted and evaluated as femoral, tibial or both.  |
|  | Arm, forearm, thigh and leg girths should be recorded especially so when an obvious difference is noted on clinical exam.  |
|  | Any deformities should be noted and recorded. The most common deformities seen in MHE 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.  |
|  | The range of motion of all joints, their stability, and any evidence of hyperlaxity, should also be noted in all cases.  |
|  | Distal vascular and neurological status (motor, sensory and reflex) should be evaluated and recorded. This includes checking of pulse in hands and feet as well as sensations.   |

## Frequency of Follow-up

- ☒ Children should be followed up at 6-9 month intervals and sooner if there are any red flags in terms of sudden increase in size of the bump, pain, tingling, numbness, weakness, visible and progressive limp, limb deformities and length discrepancies

- ☒ It is important to keep a regular follow-up of all cases even after skeletal maturity. Most patients have increased awareness of all the red flags to be watched for by this time and hence can keep a personal lookout for the same. A thorough exam can be performed by the clinician (including measurements) during the office visit. Radiographs should be repeated only when the bumps are symptomatic or growing.

**Note:** Your child's orthopaedist may recommend follow-up at different intervals, sometimes every 3 months, sometimes a year or more, and can explain why that time frame is indicated.

## Characterization of Lesions:

- **Location:** Whether the tumor is located in the limb bones, chest wall or ribs, skull, or any other sites in the body.

❶ **Pain:** Is the lesion associated with pain? If yes:

- **Intensity:** Can be assessed and documented in a lot of ways.

➡ On a pain scale of 1 to 10

➡ Pain Tracker, all of which can be used as a tool to discuss pain with a child during an examination.

- **Quality:**

➡ Do you experience pain on and off (intermittently) throughout the day, or all the time (constantly)?

➡ Does the pain occur at specific times, or with specific activities (ex. Upon waking in the morning, when walking, etc.)

➡ Is pain interfering with your general activities?

➡ Do you need to use special accommodations at work or school?

➡ Is pain affecting your mood?

➡ Do you take medications for pain, or use other treatments (i.e. heat, ice, rest). If so, are these treatments effective?

➡ Tumor pain is often unrelenting, progressive, and often present during the night

➡ Is there any shooting pain? (Suggestive of nerve compression)

**Radiation:** Pain radiating to upper or lower extremities or complaints of numbness, tingling or weakness suggest neurologic compression and requires appropriate workup.

**② Onset:**

- How was the tumor noticed?
- Was there any history of trauma?
- When did the pain actually start?

**③ Duration:**

- What has been the duration of this new lesion?
- How long have the other lesions been around?

**④ Progress:** Whether the exostosis has remained the same, grown larger, or gotten smaller?

**⑤ Associated symptomatology:**

- **Gait and posture** disturbances (especially during follow-up of skull or spinal lesions and in cases of limb-length discrepancies and deformities)
- Any specific history of back pain. If yes, its complete characterization.
- Change in **bladder or bowel habits** (for evidence of spinal lesions causing cord compression)
- **Gynecologic** function alterations in girls with pelvic lesions
- **Scoliosis** may be associated with spinal lesions and may need to be monitored

**Night pain** if present is a worrisome symptom and needs complete evaluation. Night pain is different than chronic pain in that the pain is not constant and characteristically wakes the patient from sound sleep. Chronic pain on the other hand is persistent and would interfere with the sleep pattern by making the patient restless. Chronic night pain is especially common in MHE cases where the location of the bump may cause pressure on the exostoses when lying down. Soft beds, air cushions, lateral positioning and frequent turning may prove to be helpful in these cases.

- **Neurologic symptoms** may be associated spinal or skull lesions. More commonly, local compression of peripheral nerves due to expanding lesions is encountered in arms and legs. In addition, several cases of Reflex Sympathetic Dystrophy (RSD) following MHE surgeries to knees and wrists

have been noted. Many patients also experience other nerve-related symptoms following surgery, including long-lasting pain and sensitivity around surgical sites long after incisions have healed.

**Bursa formation** and resulting bursitis may occur as a result of the exostoses and should be recorded. A bursa is a fibrous sac lined with synovial membrane and filled with synovial fluid and is found. The function of a bursa is to decrease friction between two surfaces that move in different directions. Therefore, you tend to find bursae at points where muscles, ligaments, and tendons glide over bones. These bursae can be either anatomical (present normally) or may be developmental (when the situation demands). The bursae can be thought of as a zip lock bag with a small amount of oil and no air inside. In the normal state, this would provide a slippery surface that would have almost no friction. A problem arises when a bursa becomes inflamed. It loses its gliding capabilities, and becomes more and more irritated when it is moved. Bursitis can either result from a repetitive movement or due to prolonged or excessive pressure.



## Diagnostic work-up

### Physical examination.

A thorough physical examination of the patient is extremely important in the assessment of MHE patients.

### Radiographs

High quality plain radiographs (X-rays) (anteroposterior and lateral views) should be ordered in cases presenting with exostoses. Standing postero-anterior and lateral views of the entire spine on a three-foot cassette should be ordered when spinal lesions are suspected. Special views like tangential views of the scapula may need to be ordered in some cases. Plain films help to localize the lesion and give a fairly good idea about its size and dimensions in 2 planes. Also scanograms help to assess the extent of limb-length discrepancy and its localization. Oblique views of the spine and special skull views may be ordered in suspected cases.

### Advanced Imaging

**Radionuclide bone scan** (bone scan) is sensitive to pathologies causing increased bone activities within the skeleton. In combination with SPECT (single photon emission computed tomography), it gives excellent localization of the area of increased uptake. This is extremely useful in MHE to locate multiple lesions, especially those that are situated in deeper areas not amenable to clinical palpation. Further imaging if required, can then be focused.

**Thallium and PET (positron emission Tomography) scans** are also modalities that can help define the tumor metastasis especially in those rare cases of malignant degeneration.

### Computed Tomography (CAT / CT scan)

CT scans are useful in visualizing the bony architecture particularly as an adjunct to plain radiographs or bone scans. Thin slice CT cuts may be necessary in small lesions. Two and three-dimensional reconstructions are possible and add to the information. Rarely the CT may be combined with the myelogram to effectively

delineate the size of the lesion especially for intraspinal lesions.

### **Magnetic Resonance Imaging (MRI)**

This is an excellent modality for defining the spinal cord, nerve roots, soft tissue structures and cartilage. Cortical bone is not seen as well as compared with CT. Cartilage caps of the exostoses and their compression effects on soft-tissues, nerves and adjacent vessels can be very well delineated. It is a study of choice in suspected cases of malignant transformation. MRI studies must be reserved for those cases in which clinical signs and symptoms deem them appropriate. Clinicians must make a point to communicate clinical information and suspected differential diagnosis to the radiologists.

### **Other Diagnostic Tools**

#### **Ultrasound**

May be necessary to diagnose compression of arteries. The principle for ultrasound, or ultrasonography, is the same as for underwater sonar or echo sounding. An apparatus sends an ultrasonic wave through the body at a speed of about 1,500 meters per second. At the interface between two types of tissue, the wave will be refracted or 'broken up', and part of the wave will be reflected back and detected by the apparatus. The rest of the ultrasonic wave continues deeper into the body, and is reflected as an echo from the surface of tissues lying further inside the body. How much is reflected depends on the densities of the respective tissues, and thus the speed of the sound wave as it passes through them. The time taken for the reflected wave to return indicates how deep the tissue lies within the body. In this way, one obtains a picture of the relative locations of the tissues in the body, in the same way that one may visualize the contours of a school of fish with sonar. An ultrasound can help ascertain the status of the blood flow through the arteries as well and is therefore important for assessment of suspected compression.

#### **EMG (Electromyography, myogram)**

May be necessary in cases of suspected nerve damage

#### **What is EMG**

**Electromyography (EMG)** is a test that measures muscle response to nervous stimulation (electrical activity within muscle fibers).

#### **How the test is performed**

A needle electrode is inserted through the skin into the muscle. The electrical activity detected by this electrode is displayed on a monitor (and may be heard audibly through a speaker)

Several electrodes may need to be placed at various locations to obtain an accurate study. After placement of the electrode(s), you may be asked to contract the muscle (for example, by bending your arm). The presence, size, and shape of the wave form (the action potential) produced on the monitor provide information about the ability of the muscle to respond when the nerves are stimulated.

Each muscle fiber that contracts will produce an action potential, and the size of

the muscle fiber affects the rate (frequency) and size (amplitude) of the action potentials. A nerve conduction velocity test is often done at the same time as an EMG.

### **Why the test is performed**

EMG is most often used when people have symptoms of weakness and examination shows impaired muscle strength. It can help to differentiate primary muscle conditions from caused by neurologic disorders. EMG can be used to differentiate between true weakness and reduced use due to pain or lack of motivation.

### **Histology**

Clinical examination and Imaging findings can help establishing the diagnosis in most cases.

**Biopsy** should be performed when a malignant change is suspected.

### **Laboratory evaluation / Genetic Testing (also refer to the genetics chapter)**

#### **Test methods:**

Sequence analysis of the EXT1 and EXT2 genes are offered as separate tests. Using genomic DNA obtained from buccal (cheek) swabs or blood (5cc in EDTA), testing of EXT1 proceeds by bi-directional sequence analysis of all 11 coding exons. The EXT2 gene consists of 15 exons, and all coding exons (2-15) are sequenced in the analysis.

#### **Test sensitivity:**

In patients with MHE, mutations are found in approximately 80% of individuals. Of those in whom mutations are identified, 70% of the mutations are found in the EXT1 gene and the remaining 30% in the EXT2 gene. Thus, the method used to screen the EXT1 is expected to identify approximately 60% of mutations in MHE. In individuals who are found to be negative on analysis of the EXT1 gene, screening of the EXT2 gene will identify the molecular basis of the disease in a further 25% of affected individuals. To date, there are no known distinguishing features within the clinical diagnosis of MHE known to predict which gene is more likely to have a mutation. Multiple exostoses can be associated with contiguous deletion syndromes, which are not detected with these methods.

### **How MHE Can Affect Each Part of the Body**

MHE usually manifests during early childhood more commonly with several knobby, hard, subcutaneous protuberances near the joints. The likelihood of involvement of various anatomical sites as observed in a large series is as follows:

Anatomical location	Percentage of involvement
Distal femur	70
Proximal tibia	70
Proximal fibula	30
Proximal Humerus	50
Scapula	40
Ribs	40
Distal radius and ulna	30
Proximal femur	30
Phalanges	30
Distal fibula	25
Distal tibia	20
Bones of the foot	10-25

## The Skull

Lesions in the skull, although reported are extremely rare. Mandibular osteochondromas, typically of the condyle, skull wall lesions and even intracranial lesions have been reported.

### Affects of MHE on Skull:

Exostoses can cause problems if they compress or entrap cranial nerves or cause extrinsic compression on the brain. Effects can range from bumpy external lesions that cause cosmetic problems, compression of adjacent structures, cranial nerve involvement and even focal neurological deficits due to compression. Even seizures are likely due to intracranial lesions.

### Diagnostic Procedures:

The orthopedist will manually feel for exostoses along the outer table of the skull, check movements of the mandible and also of the upper cervical spine. The orthopedist will also check cranial nerve function and perform a thorough neurological evaluation. X-rays or other imaging tests including CT and MRI may be ordered.

### Possible Treatment Options:

- ☒ Minor lesions on the outer table of the skull that are flat can sometimes be closely observed
- ☒ Bigger lesions on the skull, mandibular lesions causing TM joint instability, and intracranial lesions causing pressure signs may need to be removed by neurosurgical intervention
- ☒ Upper cervical spinal tumors, especially of the atlanto-occipital region may be dealt with by orthopedists. Decompression and or stabilization may be performed as required

## What Parents Should Watch Out For:

- ☒ Pain. Is your child experiencing pain from exostoses?
- ☒ Visible lumps on the face or skull
- ☒ Any symptoms of tingling, numbness, weakness in the hands or legs suggestive of focal deficits
- ☒ Visible lumps on the face or skull. Episodes of seizures or findings of cranial nerve involvement like altered smell, taste, ringing in ears etc
- ☒ Problems in chewing, restricted motion of the jawbone or instability of the mandible
- ☒ Parents can ask dentists and orthodontists to be on the lookout for signs suggestive of jawbone instability or joint involvement during their office visits especially in symptomatic cases

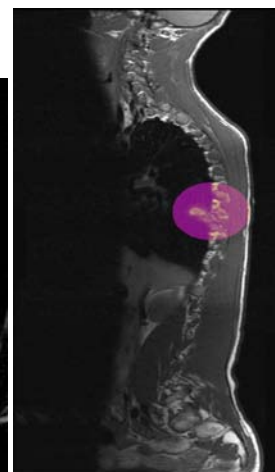
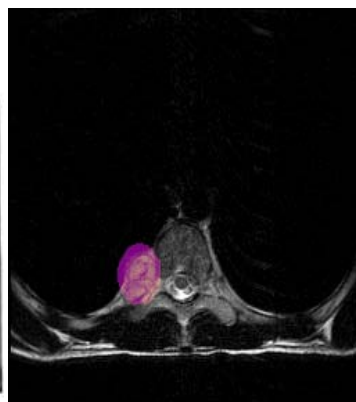
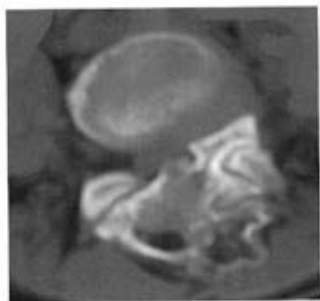
## Spine

The spine extends from the base of the skull to the tailbone. Spinal exostoses are rare (Figure 1). Spinal cord impingement is also a rare, but documented, complication of MHE. Cervical, thoracic or lumbar region can be affected. Scoliosis secondary to spinal osteochondromas and instability has been reported.

- Cervical Spine
- Lumbar Spine
- Thoracic Spine



Figure 1



## Affects of MHE on the Spine:

More views of the spine can be seen on the (*MHE Research Foundation website in the image gallery*) This section of the body is not commonly involved with MHE. Involvement of isolated vertebrae has been noted. Affects can range from instability to neural root or cord compression that can manifest as tingling,

numbness or weakness in the involved roots or even major neurological deficits like paraparesis or quadriparesis in untreated cases. Rarely compression effects in the form of dysphagia, intestinal obstruction or urinary symptoms may occur.

### **Diagnostic Procedures:**

With any of the red flags mentioned earlier, the orthopedist will perform a thorough spinal and neurological evaluation. Plain x-rays of the spine and if required, advanced imaging may be performed. The presences and extent of the lesion are best delineated with CT, while MRI of the spinal cord demonstrates the area of spinal cord impingement. In rare cases of peripheral nerve compression electromyography may be performed to check status of the nerve.

### **Possible Treatment Options:**

- ☒ Minor lesions not causing compressive symptoms or neurologic manifestations may be kept under close observation
- ☒ Progressive scoliosis and spinal instability may need to be treated with surgical stabilization involving spinal fusion

### **What Parents Should Watch Out For:**

- ☒ Any red flags in terms of tingling, numbness, weakness, night pain or bladder and bowel changes and get them evaluated
- ☒ Any deformity in the spine or evidence of shoulder or pelvic imbalance
- ☒ Gait or posture disturbances. Remember that gait and posture disturbances can be caused by hip or leg exostoses as well (due to either limb-length discrepancy or deformity) and do not necessarily mean tumors in the spine. In any case evaluation by a clinician is important

### **Ribs and Sternum, Affects of MHE on the ribs and sternum:**

The typically flat bones of the ribs are prone to effects of MHE, with approximately 40% of MHE patients having rib involvement. Prominent chest wall lesions are common although intrathoracic lesions including rare presentations like spontaneous hemothorax (build-up of blood and fluid in the chest cavity) as a result of rib exostoses have been described. Typically, these lesions create issues of cosmesis due to their obvious visibility. Other symptoms may include shortness of breath and other breathing difficulties, pain when taking a deep breath, when walking or exercising, or pain from exostoses "catching".

### **Diagnostic Procedures:**

The orthopedist will probably manually feel for exostoses along the chest wall and the ribcage. Size and extent of the lesions are noted. A thorough pulmonary evaluation is warranted in all cases when specific symptoms of cough, chest pain or breathing problems are encountered. X-rays or other imaging tests may be ordered.

## Possible Treatment Options:

- ☒ Minor bumps can sometimes be kept under observation
- ☒ Cosmetic problems, rapid increase in size, large size, and signs of compression are some indications for early removal
- ☒ Consult may be required with specialists:

Pulmonary: when there are severe breathing difficulties with increasing chest pain.  
Thoracic surgeons: when intrathoracic (within the chest wall) exostoses may need to be excised.

## What Parents Should Watch Out For:

- ☒ Breathing difficulties, shortness of breath.
- ☒ Pain when taking deep breath.

## Shoulder girdle

The scapula is a fairly common site (40%) of involvement in MHE. The lesions may be located on the anterior or posterior aspect of the scapula. Anterior scapular lesions may lead to discomfort during scapulothoracic motion. Winging of the scapula due to exostoses has been described. Clavicle (collar bone) involvement has also been described (5% cases).

### What is winging?

The scapula (also known as shoulder blade) is a triangular flat bone that is located in the upper back and takes part in forming the shoulder joint. The scapula usually lies flat on the chest wall without any prominence. Winging of the scapula is a phenomenon when a part of the scapula including the inferior angle becomes prominent either at rest or during movements.

### The two most common causes for this are

- ① Exostosis on the inner (chest wall) aspect of the scapula
- ② Damage to the nerve (long thoracic) causing weakness or paralysis of muscles (serratus anterior) attached to the scapula

### Diagnostic Procedures:

The orthopedist will probably manually feel for exostoses along the outer aspect of the shoulder blade. Some limited areas of the inner aspect are amenable to clinical examination. Range and feel of the scapulothoracic motion is helpful in clinical assessment. It is important to check individual groups of scapular muscles to rule out nerve compression leading to winging of scapula. X-rays (including special tangential views of the scapula) or other imaging tests may be ordered.

## Possible Treatment Options:

- ☒ Both outer aspect lesions and inner ones may need excision in symptomatic cases. Smaller lesions on outer aspect amenable to clinical palpation may be observed with regular clinical follow-up

## What Parents Should Watch Out For:

- ☒ Crunching or crackling sound when moving that area.
- ☒ Pain.
- ☒ Tingling, numbness.

## Arms

- ☒ Upper Arm (X-rays) (Humerus)
- ☒ Elbow
- ☒ Forearm (Radius and Ulna)
- ☒ Wrists



The arm bone is called the humerus while the forearm bones are the radius (curved bone) and the ulna (straighter bone of the two). To view more x-rays please refer to the *MHE Research Foundations website image gallery*.

Osteochondromas of the arm are often readily felt but rarely cause neurologic dysfunction. Osteochondromas of the upper extremities frequently cause forearm deformities. The prevalence of such deformities has been reported to be as high as 40-60%. 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 well-described sequelae in the context of these deformities.

The length of forearm bones inversely correlates with the size of the exostoses. 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. Thus, the skeletal growth disturbance observed in MHE is a local effect of benign growth. Exostoses in the forearm are known to involve both the radius and the ulna. Since movements of the forearm (pronation and supination) are dependant on the radius moving in an arc of motion around the ulna, mobility may be restricted depending upon the severity of presentation. Also the lower end radius exostoses can lead to compression of the median nerve (in a closed space at the level of the wrist called the carpal tunnel) and present with weakness, tingling and numbness in the hand. Exostoses in the carpal bones can seriously hamper the wrist motion and cause pain.

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.

### Diagnostic Procedures:

The orthopedist will clinically feel for exostoses along the arm, elbow and forearm, and check range of motion ("ROM") by moving the arm in different directions. The orthopedist will also check measurements on each arm and forearm to see if there is a difference. X-rays or other imaging tests may be ordered.

### Possible Treatment Options:

- ☒ 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. Minor lesions can sometimes be observed with careful follow up.

- ☒ Bowing and some length discrepancies can be treated with a surgical procedure called "stapling," where surgical staples are inserted into the growth plate of the bone growing faster than the other. This will hopefully give the slower growing bone the chance to "catch up" and the forearm will straighten over time.

- ☒ Limb Lengthening with a fixator

- ☒ Osteotomy

- ☒ Resection of the radial head.

- ☒ Excision of exostoses

- ☒ Non-surgical measures for treatment of soft-tissue compression, irritation or inflammation (anti-inflammatories, heat, rest, etc.) Adaptive devices to aid those with shortened.

### What Parents Should Watch Out For:

- ☒ Any red flags in terms of sudden increase in size of swelling, pain, nerve compression, tingling, numbness, or weakness
- ☒ Possibility of exostoses irritating or catching on overlying tissue, such as muscles, tendons, ligaments, or compressing nerves
- ☒ Loss of range of motion
- ☒ Pain
- ☒ Difficulty and/or pain when raising arm(s), lifting, carrying

### Hands and Fingers

Hand involvement in MHE is common. Fogel et al. observed metacarpal involvement and phalangeal involvement in 69% and 68%, respectively, in their series of 51 patients. In their series of 63 patients, Cates and Burgess found that patients with MHE fall into two groups: those with no hand involvement and those with substantial hand involvement averaging 11.6 lesions per hand. 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.

### Diagnostic Procedures:

The orthopedist will manually feel for exostoses in the hands and check range of motion ("ROM") in different directions. X-rays or other imaging tests may be ordered.

### Possible Treatment Options:

- ☒ Isolated lesions growing rapidly, or interfering with the smooth motion of tendons or joint motion may need to be excised. Multiple surgeries for small, insignificant lesions is usually not advocated
- ☒ Occupational therapy, physical therapy
- ☒ Use of pencil grips, laptop computers, and other adaptive devices

### What Parents Should Watch Out For:

- ☒ Complaints of pain when writing
- ☒ Some children will not complain of pain, but will have poor penmanship, write slowly, avoid writing, etc. Parents should also observe how the child holds writing and eating utensils.
- ☒ Difficulty in rotating hand(s)

## Pelvic Girdle (Hips and Pelvis)



Osteochondromas of the proximal femur may lead to progressive hip dysplasia. There have been reported cases of acetabular dysplasia with subluxation of the hip in patients with MHE. This results from exostoses located within or about the acetabulum that may interfere with normal articulation.

Pelvic lesions may be found on both the inner as well as outer aspect of the pelvic blades. Large lesions may cause signs of compression, both vascular and neurological. There have also been reports of exostoses interfering with normal pregnancy and leading to a higher rate of Cesarean sections.

### Diagnostic Procedures:

Manual palpation is sometimes very difficult in these deep lesions. The orthopedist will check range of motion ("ROM") by manipulating (moving) the leg in different directions. The orthopedist will also check measurements on each leg to see if there is a difference in limb lengths. X-rays or other imaging tests may be ordered.

### Possible Treatment Options:

- ☒ Minor length discrepancies can sometimes be effectively treated with the use of orthotics (specially made shoes or lifts that will equalize leg length)
- ☒ Bowing and some limb length discrepancies can be treated with a surgical procedure called "stapling," where surgical staples are inserted into the growth plate of the leg bone growing faster than the other. This will hopefully give the slower growing bone the chance to "catch up" and the limb will straighten over time.
- ☒ Limb Lengthening with a Fixator. Please refer to the lower limb & forearm, use of fixators chapter
- ☒ Pelvic lesions of concern may need to be surgically excised
- ☒ Osteotomies
- ☒ Hip replacement

### ***What Parents Should Watch Out For:***

- ☒ Limping
- ☒ Pain in hips, back, legs
- ☒ Pain, discomfort, difficulty in sitting
- ☒ Inability to sit "tailor" style. The position known as Indian or tailor style involves both feet
- ☒ Stiffness in hips and/or legs after sitting
- ☒ Pain and fatigue from walking

### **Legs and Knees**

- ☒ **Femur**
- ☒ **Knees**
- ☒ **Lower Leg** (Tibia and Fibula)



**Genu Valgum or Knock-knee** deformities are found in 8-33% of patients with MHE. Genu valgum is defined as a mechanical malalignment of the lower limb when the knees knock against each other and the legs are pointed away from the body. Although distal femoral involvement is common, the majority of cases of angular limb deformities are due mostly to lesions of the tibia and fibula which occur in 70-98% and 30-97% of cases, respectively. 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. Genu varum or Bowlegs may also occur in some cases. This is defined as a mechanical malalignment of the lower limb when the knees drift away from the body and the legs are bowed and close together.

### Diagnostic Procedures:

The orthopedist will probably manually feel for exostoses along the leg, and check range of motion ("ROM") by manipulating (moving) the leg in different directions. The orthopedist will also check measurements on each leg to see if there is a difference. X-rays or other imaging tests may be ordered.

### Possible Treatment Options:

- ☒ Minor length discrepancies can sometimes be effectively treated with the use of orthotics (specially made shoes or lifts that will equalize leg length)

Bowing and some limb length discrepancies can be treated with a surgical procedure called "stapling," where surgical staples are inserted into the

- ☒ growth plate of the leg bone growing faster than the other. This will hopefully give the slower growing bone the chance to "catch up" and the limb will straighten over time.

- ☒ Limb Lengthening with a Fixator

- ☒ Excision of exostoses

- ☒ Osteotomy

### What Parents Should Watch Out For:

- ☒ Any red flags in terms of sudden increase in size of swelling, pain, nerve compression, tingling, numbness, or weakness

- ☒ Possibility of exostoses irritating or catching on overlying tissue, such as muscles, tendons, ligaments, or compressing nerves

- ☒ Leg cramps, bluish color, difference in skin temperature may indicate compression of a artery (most often the popliteal artery, located behind the knee)

- ☒ Compression of the peroneal nerve, which runs along the outside of the leg, can cause a condition known as "drop foot", in which the foot cannot voluntarily be flexed up. Compression can be caused by exostoses growth, or as a complication of surgery.

- ☒ Limping, pain when walking

- ☒ Bowing of leg(s)

- ☒ Exostoses on inside of legs bumping into each other

- ☒ Exostoses interfering with normal movements, either by blocking movement

or by causing pain (bending, sitting, walking up or down stairs)

- ☒ Pain and fatigue when walking
- ☒ Gait problems (awkwardness, limping, slow movements, etc.)

## Ankles



Valgus deformity of the ankle is also common in patients with MHE and is observed in 45-54% of patients in most series. This valgus deformity can be attributed to multiple factors including shortening of the fibula relative to the tibia. 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.

### Diagnostic Procedures:

The orthopaedist will probably manually feel for exostoses along the leg, and check range of motion ("ROM") by manipulating (moving) the leg in different directions. The orthopaedist will also check measurements on each leg to see if there is a difference. X-rays or other imaging tests may be ordered.

### Possible Treatment Options:

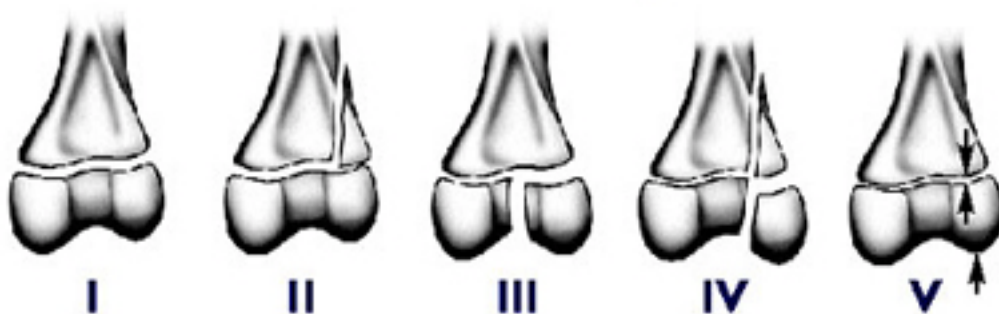
- ☒ Minor length discrepancies can sometimes be effectively treated with the use of orthotics (specially made shoes or lifts that will equalize leg length).
- ☒ Bowing and some limb length discrepancies can be treated with a surgical procedure called "stapling," where surgical staples are inserted into the growth plate of the leg bone growing faster than the other. This will hopefully give the slower growing bone the chance to "catch up" and the limb will straighten over time.
- ☒ In more advanced cases, excision of exostoses with 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.

- ✓ 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).
- ✓ Supramalleolar osteotomy of the tibia has also been used effectively to treat severe valgus ankle deformity.
- ✓ Growth of exostoses can also result in tibiofibular diastasis that can be treated with early excision of the lesions.

### What Parents Should Watch Out For:

- Limping, pain when walking. Recurrent falls and instability while walking on uneven surfaces. Parents should be aware that falls could result in what are known as Salter-Harris Fractures / (Growth plate fractures) this has been
- ✓ seen to occur in children with MHE / MO / HME. If your child falls and the pain is occurring around the growth plate area of the joint, this should be checked by your orthopaedic doctor. As these type of fractures can also lead to bone deformity

### The Salter-Harris Classification of Growth Plate Injuries



Graphic provided by [http://www.niams.nih.gov/Health\\_Info/Growth\\_Plate\\_Injuries/graphics/growth-plate.jpg](http://www.niams.nih.gov/Health_Info/Growth_Plate_Injuries/graphics/growth-plate.jpg)

### Feet and Toes

Osteochondromas may occur in the tarsal and carpal bones, however they are often less apparent. Relative shortening of the metatarsals, metacarpals, and phalanges may be noted.

### Diagnostic Procedures:

Plain radiographs are probably more useful in defining the extent of involvement of the small bones of the feet in MHE. Other imaging studies may be ordered as and when required.

## Possible Treatment Options:

- ✓ Large bumps can be surgically excised when symptomatic.
- ✓ Deformities of the foot (like hallux valgus) may be corrected by stapling of the growing epiphysis in younger children or by surgical osteotomy in older patients.

## What Parents Should Watch Out For:

- ✓ Compression of the peroneal nerve, which runs along the outside of the leg, can cause a condition known as “drop foot”, in which the foot cannot voluntarily be flexed up. Compression can be caused by exostoses growth, or as a complication of surgery.

## In general “What Parents Should Watch Out For”

- ✓ If your child is limping, check to see if it is due to an injury, or is something that is occurring and continuing without obvious reason. Limping may signal a limb length discrepancy or other problem.
- ✓ Bowing of one or both legs.
- ✓ Mobility problems. Is your child experiencing pain when walking or running? Pain. Is your child experiencing pain from exostoses that bump each other?
- ✓ Is your child experiencing pain during certain activities, or pain at night. If so, keep a pain diary.
- ✓ Any red flags in terms of sudden increase in size of swelling, pain, nerve compression, tingling, numbness, or weakness.

## What Adults Should Be Aware of:

- ✓ Sudden growth in an existing exostosis and pain can be symptomatic of a malignant transformation. It is smart to check out any changes with your orthopaedist. However, it is important to remember that chondrosarcoma is rare. Refer to chondrosarcoma chapter.
- Years of wear and tear on joints can result in chronic pain. There is also the possibility of exostoses irritating or catching on overlying tissue, such as muscles, tendons, ligaments, or compressing nerves. Possible Treatment
- ✓ Options for these common problems, include pain medications, physical therapy (including stretching, strengthening and modalities), heat, rest, bracing (supportive orthosis acting as load sharing devices) etc.

## **Glossary of terms and procedures:**

**Synonyms of multiple exostoses:** 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.

**Anterior:** Situated in the front; forward part of an organ or limb

**Ball and socket joints:** Movable (synovial) joints, such as hips and shoulders, that allow a wide range of movement.

**Bilateral:** having two sides or pertaining to both sides.

**Biopsy:** Take a piece of the lesion to study the histological characteristics.

**Cartilage:** Form of connective tissue, more elastic than bone, which makes up parts of the skeleton and covers joint surfaces of bones.

**Coxa-valga:** When the thighbones are drawn farther apart from the midline due to an increase in the neck-shaft angle of the femur.

**Coxa-vara:** When the thighbones are drawn closer to the midline due to a decrease in the neck-shaft angle of the femur.

**Dislocation:** When the normal articulating joint surfaces have lost total contact.

**Distal:** Away from the midline or the beginning of a body structure (the distal end of the humerus forms part of the elbow).

**Epiphysiodesis:** To surgically stop the growth of the growing end of the bone either temporarily or permanently.

**Excision:** To surgically remove the lesion.

**Genu-valgum:** Knock-knees.

**Genu-varum:** Bowlegs.

**Hinge joints:** movable joints, such as knees and elbows, that allow movement in one direction.

**Limb-lengthening:** Process of increasing the length of bones using one of the various devices.

**LLD:** Limb-length discrepancy- difference in limb lengths.

**Medial:** Pertaining to the middle or toward the midline.

**MHE:** An autosomal-dominant disorder manifested by multiple osteochondromas and frequently associated with characteristic skeletal deformities.

**Osteochondromas:** Cartilage capped tumors found commonly at rapidly growing ends of bones.

**Osteotomy:** The surgical division or sectioning of a bone.

**Pedunculated:** Lesion with a stalk connecting it to the main bone.

**Posterior:** Situated in the back; back part of an organ or limb

**Proximal:** Near the midline or beginning of a body structure (the proximal end of the humerus forms part of the shoulder).

**Sessile:** Lesion without a stalk connecting it to the main bone.

**Stapling:** Process of insertion of a mechanical device (staple) following surgical intervention.

**Subluxation:** When the joint surfaces are still facing each other but not totally in contact.

# Multiple Exostoses / Multiple Osteochondroma of the Forearm

By Dror Paley M.D.,  
Director of the [Paley Advanced Limb Lengthening Institute](#)  
at  
St. Mary's Hospital in West Palm Beach, Florida.

Located on the MHE Research Foundations website is a companion educational video, **Multiple Hereditary Exostoses of the Forearm** by Dr. Paley

## Introduction

The forearm consists of two bones (radius and ulna) and six joints (elbow: radio-capitular and ulno-humeral; wrist: radio-carpal and ulno-triquetral; radio-ulnar: proximal and distal). Unlike the relationship between the tibia and fibula in the lower extremity the radius and ulna move functionally relative to each other to produce the movement of supination and pronation. Relative to the elbow they move together (flexion and extension). Although most wrist motion and stability comes from the articulation between the radius and the carpus, the ulna provides support for the ulnar side and prevents excessive ulnar deviation of the hand. The relationship between the radius and the ulna is therefore one of the most functional relationships between any two bones.

Exostosis formation of either bone can easily interfere in the function of the elbow, wrist or forearm rotation. Since osteochondromas form from the growth plates they are usually found at the ends of the bones but migrate towards the shaft of the bone with growth.

**Ulnar Osteochondromas:** osteochondromas most commonly form from the distal growth plate. Unlike those of the radius the ulnar exostoses are **typically sessile (no stalk)** while those of the radius are often **pedunculated (on a stalk)**. The osteochondromas of the ulna often lead to delayed growth of the ulna relative to the radius. The radius gradually gets longer than the ulna. The slower growing ulna tethers the growing radius leading to increased tilt of the radius towards the ulna with increasing ulnar deviation of the wrist. Over time, the discrepant rate of growth leads to subluxation and then dislocation of the proximal end of the radius (radial head) from the elbow (radio-capitellar joint). Dislocation of the radial head from the joint causes the upper end of the radius to deform into valgus (bent position). Occasionally an osteochondroma can develop

from the ulna side of the proximal radio-ulnar joint. This can also contribute to dislocation of the radial head by pushing the radial head laterally.

**Radial Osteochondromas:** osteochondromas from the radius can be divided into those that protrude towards the ulna and those that don't. The latter don't impede supination-pronation motion, while the former do. The radius and ulna may develop 'kissing exostoses' that meet in the interosseous space.

**Distal radius deformity:** the distal radius has a normal inclination towards the ulna of 23°. In MHE the slower growing ulna may tether the distal radius on the ulnar side leading to increased distal radial tilt. This increased tilt appears as ulnar deviation of the hand. With time the carpus will subluxate ulnarly and proximally.

**Proximal radius deformity:** The ulnar tether also exerts a dislocating force on the radio-capitellar joint. As the radial head subluxes it comes to rest against the lateral condyle of the humerus. To adapt to this chronic position the radial neck may grow into valgus. With time, the radial head may completely dislocate and protrude posteriorly.

**Length discrepancy:** The entire forearm is shorter than the other side. The shortening is predominantly in the ulna. Some shortening is also present in the radius.

Clinical signs and symptoms: Patients are limited in their forearm rotation range of motion. The wrist is usually ulnarly deviated. There may be a prominence or bump if the radial head is subluxed or dislocated. This may be tender to being bumped. Elbow flexion and extension is usually not affected. A flexion deformity of the elbow may be present.

## **Treatment considerations**

Exostoses that are obviously impeding forearm rotation (e.g. kissing exostoses, are usually resected. It is important to do this via two separate incisions to avoid a cross union between the radius and ulna. Lengthening and deformity correction can be performed as the first stage in the absence of exostoses that limit motion, or as the second stage if exostoses are resected first.

## **Lengthening Reconstruction Surgery (LRS):**

LRS refers to distraction surgery using external fixation to lengthen and correct deformities of the forearm. The problem in MHE ranges from simple to complex.

**Simple cases:** In simple cases, the primary deformity is relative shortening of the ulna. The radial tilt is minimal and does not need to be addressed. There is no subluxation/dislocation of the radial head. The problem is therefore just shortening of the ulna. If this is left untreated the secondary deformities of the radius will develop. The treatment is to perform an isolated lengthening of the ulna. I prefer to do this with a circular external fixator even though the lengthening is linear. A circular fixator allows simultaneous fixation of the radius to the ulna. Without fixation of the radius, lengthening of the ulna will transport the radial head distally. This occurs because of the tough interosseous membrane between the radius and the ulna. The osteotomy of the ulna is usually at its proximal end. This allows correction of any flexion deformity of the ulna (elbow) and leads to faster healing than if the osteotomy is made through the mid-diaphyseal (middle) section of the ulna.

**Complex cases:** In more complex cases the surgical plan includes correction of the distal radial deformity and or radial head dislocation. A circular external fixator is used. Proximally both the radius and ulna are fixed. The ulnar osteotomy is made proximally and the radial osteotomy is made distally. This type of frame simultaneously corrects shortening of the ulna and tilt of the distal radius. If the radial head is dislocated then the treatment is staged. The first step is to lengthen the ulna with a pin connecting the radius and ulna distally. This transports the radius distally and reduces the radial head. If the radial head does not reduce spontaneously then at a second stage surgery the radio-capitellar joint is opened and the radial head reduced at surgery and is held with an olive wire. If there is both distal radial tilt and dislocation of the radial head then the radial head is reduced first and then at a second stage the wire pulling the radius and ulna distally is removed and the distal radius osteotomized for deformity correction and lengthening.

With staged surgeries many of the deformities of MHE of the forearm can be corrected. Combined with removal of the obstructing exostoses improved range of motion of forearm rotation is obtained.

Does hemiepiphysiodesis stapling have a role in MHE? I have no experience with this in the upper extremity. Theoretically, it should work for the distal radius. We are considering correction of the distal radial tilt by stapling in combination with over lengthening of the ulna. Over lengthening of the ulna can help delay recurrence. Over lengthening of up to 2 cm is practical. Fixation of the hand is not required if the lengthening of the radius is less than 3 cm.

# **Multiple Exostoses / Multiple Osteochondroma of the Lower Limb Guide**

**By Dror Paley M.D.,**

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**at**

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**Located on the MHE Research Foundations website is a companion educational videos, Biology of Limb Length, Limb Lengthening Methods by Dr. Paley**

## **Multiple Osteochondromas**

There are a variety of problems related to the exostoses of Hereditary Multiple Osteochondromas. The majority of these problems relate to bothersome bony protrusions with their affect on surrounding joints, muscles, tendons, nerves, blood vessels and skin. Osteochondromas can also affect growth plates and lead to limb deformities and length discrepancies. The focus of this article will be on the limb deformities and discrepancies secondary to the multiple osteochondromas.

## **Lower Limb**

Osteochondromas are believed to bud off the growth plates. The cartilaginous cap of the osteochondroma has the same structure as the growth plate. It grows in length and width in the same fashion as a growth plate leads to growth in length and width of the end of a bone. For reasons unknown some osteochondromas tether the growth of the growth plate when they bud off. This can lead to asymmetric growth (less growth on the osteochondroma side and more growth on the opposite side of the growth plate) and consequently limb deformity. This tethering effect can also decrease overall limb growth leading to a shorter final limb length than expected. If the opposite lower limb is not as affected then the result is a lower limb length discrepancy (LLD). Although both lower limbs often appear to be equally affected by osteochondromas, LLD is not uncommon indicating that one side is more tethered at the growth plate then the other.

The tethering effect of the osteochondroma on growth is directly related to the size of the growth plate it came from. The larger the growth plate the less effect the osteochondroma has on longitudinal growth because the force of growth in the remaining healthy part of the growth plate is so great. The smaller the growth plate the greater is the tethering effect since the percent of the growth plate involved is so great. Good examples of this are the fibula in the lower limb and the ulna in the upper limb. We shall discuss the ulna in a future article. In the lower leg where there are two adjacent bones (tibia and fibula), a osteochondroma tethering the growth of one bone and not the other will lead to a deformity since

the two bones are attached together. Therefore if the fibula is growing slower than the tibia the leg will grow towards the fibula. This leads to a valgus deformity (knock-kneed) of the upper tibia and a valgus deformity of the ankle (tilted outward). Osteochondromas between the tibia and fibula can also lead to deformity of the adjacent bone. For example an osteochondroma of the distal tibia can lead to deformity of the adjacent fibula near the ankle.

Osteochondromas of the distal femur (lower end of femur near the knee), do not typically lead to any deformity or length discrepancy on their own. They protrude into the surrounding soft tissues and can lead to symptoms related to soft tissue impingement due to their bulk. On occasion they do lead to deformity of the knee which is related to the tethering of soft tissues and not to bony deformity. For example osteochondromas around the knee can lead to locking and flexion deformity of the knee joint (The knee joint catches in a certain position and will not straighten out)

Osteochondromas of the upper femur sprout off the femoral neck. Depending on the direction they come from they lead to different problems. Commonly they lead to asymmetric growth of the neck of the femur resulting in a valgus femoral neck (more vertical than usual). This is usually not a problem. Valgus of the neck of the femur is usually symmetric and therefore does not lead to a leg length discrepancy.

When the osteochondroma is too near the hip joint or if it expands the capsule of the hip joint, this can result in a hip joint contracture or subluxation. The typical hip joint contracture is fixed flexion deformity of the hip from an anterior osteochondroma. Patients present walking leaning forward with hyperlordosis of the spine (sway back) as they try and compensate for the leaning forward effect of the hip by arching their back.

Subluxation of the hip occurs due to the effect of the osteochondroma pushing the hip out of joint combined with the effect of the valgus of the femoral neck.

## **Treatment of the Lower Limb Deformities.**

### **Valgus Knee Deformity (Knock knee deformity)**

This deformity is usually in the upper tibia. There is usually a large osteochondroma involving the upper end of the fibula. The fibular osteochondroma often tethers or envelops the peroneal nerve. This is a very important nerve that is responsible for controlling the muscles that pull the foot up and out. Injury to this nerve results in a drop foot (inability to pull the foot up). Correction of the valgus deformity of the upper tibia requires an osteotomy (bone cut) of the upper tibia. All osteotomies of the upper tibia to correct valgus stretch the peroneal nerve even in patients without HME. In patients with HME and a fibular exostosis

the nerve is very tethered and stretched even before surgery. The nerve can actually be inside the bone if the osteochondroma envelops it. Therefore to correct the deformity safely the nerve must first be found above the fibula and decompressed around the neck of the fibula. The osteochondroma of the fibula should be resected. If the upper fibular growth plate is considered to be damaged beyond recovery then a segment of the fibula should be removed so that the two ends of the fibula do not join together again to prevent re-tethering of the tibia.

Only after all of this is performed can an osteotomy of the tibia be carried out safely to correct the valgus deformity. The valgus deformity can either be corrected all at once or gradually. Correcting it all at once is usually performed by taking out a wedge shaped piece of bone and then closing the wedge to straighten the tibia. This can be fixed in place with a metal plate or with an external fixator. Gradual correction is carried out by minimal incision technique to cut the bone. The correction is achieved by use of an external fixator. This is a device that fixes to the bone by means of screws or wires that attach to an external bar or set of rings.

Adjustment of the external fixator slowly corrects the deformity. This opens a wedge instead of closes a wedge of bone. This has the advantage of adding length to the leg which if the leg is short already is advantageous. This type of external fixator is also used for limb lengthening. Therefore if there is a LLD the angular correction can be performed simultaneous with lengthening. Gradual correction is safer than acute (all at once) correction for correction of the valgus deformity. Another way to address the valgus knee deformity without addressing limb length discrepancy is hemi-epiphyseal stapling of the growth plate. This is perhaps the most minor procedure possible and involves insertion of one or two metal staples on the medial side (inside) of the growth plate of the upper tibia. The metal staple straddles the growth zone on the medial side preventing growth of the medial growth plate while permitting growth on the lateral side. This allows the tibia to slowly autocorrect its alignment. It is a very slow process and may require several years. Once the tibia is aligned the staple can be removed permitting resumption of growth from the medial side. There is a small risk of damaging the medial growth plate which could lead to a varus bowing deformity of the tibia. Stapling can also be used in the distal tibia to correct the ankle deformity.

### **Valgus deformity of the ankle**

Patients complain of walking on the outer border of the foot. Viewed from behind this posture of the foot is very apparent. This deformity is often well tolerated. The lower end of the tibia tilts outwards towards the fibula. The lower end of the fibula is the lateral malleolus. It is important for stability of the ankle. Since the fibula grows less than the tibia the lateral malleolus is often underdeveloped

leading to lateral shift of the talus (ankle bone). This can eventually lead to arthritis of the ankle. Lateral tilt of the ankle joint is compensated by the subtalar joint (joint under the ankle) by inversion of the foot (turning of the foot in). Since this is a longstanding process the subtalar joint becomes fixed in this position of compensation for the ankle joint. Therefore if one tries to fix the ankle joint tilt completely the foot will end up tilted inwards and the patient will be standing on the outer border of the foot. Therefore one either has to accept the valgus ankle or correct it together with the subtalar joint fixed deformity. This is best done with a circular external fixator (Ilizarov device). This correction involves gradual correction of a minimally invasive osteotomy of the lower tibia and fibula together with distraction (pulling apart) of the subtalar joint contracture.

## **Flexion deformity of the knee**

This deformity is usually related to tethering or locking of the soft tissues around the knee by distal femoral or proximal tibial osteochondromas. The treatment involves resection of the offending exostosis and lengthening of the hamstring tendons if needed.

## **Flexion deformity of the hip / subluxation of the hip/valgus upper femur.**

This is treated by resecting the offending osteochondroma of the femoral neck. This hip capsule has to be opened to access these. At the same time to reduce the hip subluxation (hip coming out of joint) a varus osteotomy of the upper femur should be done (bending the femur inwards towards the joint). The bone can be fixed either by an internal metal plate or an external fixator.

## **Limb Length Discrepancy**

Limb length discrepancy under 2cm is usually not noticeable and does not require treatment. LLD over 2cm is usually noticed by the individual affected leading to self compensation by walking on the ball of the foot (toe down) or by tilting the pelvis and curving the spine (scoliosis). Untreated LLD can lead to lower back pain, and long leg arthritis of the hip. These take many years to develop. Individuals who compensate for LLD by walking on the ball of the foot often develop a tight Achilles tendon. The easiest way to treat LLD is by using a shoe lift. I generally prescribe a shoe lift one cm less than the LLD. Shoe lifts of up to 1cm can be easily accommodated inside a shoe. Greater than 1cm should be added to the outside of the shoe. Wearing a shoe lift prevents problems of the back, hip and ankle from developing. LLD can also be equalized surgically. This can be done by either shortening the long leg or lengthening the short leg. In children shortening the long limb is achieved by surgically closing the growth plate of the lower femur or the upper tibia prematurely (epiphysiodesis).

This is a small minimally invasive procedure with few complications. The accuracy of this method depends on the ability of the surgeon to predict the LLD at maturity and the rate of growth of the long limb. The accuracy of LLD equalization with this method is  $\pm 1\text{cm}$ . After growth of the skeleton has ceased (skeletal maturity) epiphysiodesis is no longer an option. Shortening in adults is carried out by removing a segment of the bone and fixing the bone in place with a metal rod that is inserted into the marrow cavity (locked intramedullary nail). In the femur this procedure can be done through very small incisions, and shortening up to 5cm (2 inches) can be safely achieved. In the tibia this procedure requires bigger incisions and has greater risk and is usually limited to 3cm (1.25 inches).

**Lower limb lengthening** is the other way to correct LLD and can be carried out in both children and adults and at almost any age. To lengthen a limb the bone is cut through a very small incision (1cm) and then the two ends of the bone are pulled apart at a gradual rate of 1mm/day (1/25 inch/day). Since bone is a living substance it grows new bone to repair the break. By pulling the bone apart at a gradual rate, we prevent the bone ends from joining together. Instead new bone is formed in the growing gap between the bone ends. Once the desired lengthening is achieved the bone is held in place until it joins together. The new bone that was formed in the gap becomes stronger as calcium accumulates in it.

Eventually this new bone achieves the strength of normal bone. There are various devices that are used for limb lengthening. The majority of these are external fixators. An external fixator is an external frame or brace that attaches directly to the bone by means of thin (1.8mm- 1/16") tensioned wires or thicker (6mm- 1/4") screws (half-pins). The frame of the fixator is either shaped like a bar (monolateral fixator: e.g Orthofix, EBI, Wagner, monotube) or has rings and arches (circular fixator: Ilizarov, Taylor Spatial Frame, Sheffield). More recently these systems have become hybridized and have elements of both monolateral and circular fixators.

The circular fixators can be attached to the bone by means of wires that go from one side of the limb to the other passing through the skin on one side, then through the bone and then exiting the skin on the other side. Wires have much smaller diameters than half-pins and achieve their strength by being tensioned across the ring, like tensioning a guitar string. Half pins are of much larger diameter and only pass through the skin on one side. They fix to the bone by means of a screw-like thread. To lengthen the limb the fixator has a screw mechanism which allows for small adjustments that pull the bone apart. The bone is pulled apart because the fixator which is attached to the bone above and below the break in the bone, lengthens as the screw mechanism is turned. The typical lengthening rate is 1/4mm, 4 times a day, for a total of 1mm/day. There is even a motorized attachment which can be used for lengthening (Autogenesis). This

lengthens at the same rate of 1mm/day divided into hundreds of small lengthenings. This may reduce the pain of lengthening. It is also more gentle on the soft tissues (nerves, muscles) that must stretch and grow as the bone is pulled apart.

The most common complication and care with external fixator lengthening is superficial pin infection. (Refer to fixator care guide) This minor complication is to be expected. It is also easily treated by taking oral antibiotics at the first sign of infection (redness, tenderness, and drainage around a pin site). Deeper infection of the soft tissues and bone is quite rare, but if it occurs usually requires removal and possible replacement of the problem pin, IV antibiotics and sometimes surgery to debride (remove dead tissue) the soft tissue and bone. Other complications include tightness of muscles which can limit the range of motion of the adjacent joints or even pull the adjacent joints into a fixed position that interferes with function (e.g. equinus contracture of the ankle (fixed toe down position) is due to tightness of the Achilles tendon that develops during lengthening).

To prevent problems with joints and muscles it is essential to do daily range of motion and stretching exercises with physical therapy, and to maintain that stretch by using foot or knee splints. Sometimes it is necessary to either immobilize a joint by extending the external fixation across the joint to hold the joint in a functionally good position (e.g. foot fixation at 90° with tibial lengthening to prevent equinus). In some cases it may be necessary to surgically lengthen some of the tendons or fascia to prevent or treat contractures (e.g. Achilles tendon lengthening). Bone complications can also occur. These include too rapid or too slow bone formation. Too rapid formation (premature consolidation) can prevent further lengthening and requires rebreaking the bone to continue lengthening. To prevent this, the lengthening rate may have to be increased. Poor bone formation can also occur (delayed consolidation). This requires more time in the external fixator until the bone is fully healed. Complete or partial failure of bone formation leads to a bone defect and may require a bone graft to get the bone to heal.

There are two phases to the lengthening process. The first is the distraction phase when the bone is being pulled apart at one mm per day. The second is the consolidation phase when the bone is hardening while it is being held in place by the external fixator. The fixator cannot be removed until the bone is completely healed. If the fixator is removed before that time the bone will bend, shorten and/or break. The best way to tell if the bone is fully healed is by x-ray. Even with x-rays it is not uncommon to misjudge the strength of the bone and remove the fixator prematurely. In many cases we apply a cast for an additional month of protection to minimize the risk of refracture. It is better to leave the fixator on an extra month than to take it off a day too early. Patients are often impatient at this stage and push their doctors to take the frame off. An experienced limb

lengthening surgeon turns a deaf ear to these frustrations and refuses to remove the frame until the x-rays suggest that the bone is strong enough that it will not break or bend upon removal. Most of the complications of lengthening occur during the distraction phase or after removal. Few complications other than pin infection arise during the consolidation phase.

External fixator lengthening has been the standard for the past one hundred years of the history of limb lengthening. In the past decade internal lengthening devices have emerged. These permit gradual lengthening by means of a fully implantable telescopic intramedullary rod (a metal rod that fits inside the marrow cavity of the bone). While there are several of these devices in use worldwide, there is only one at present FDA approved in the USA. This is called the Intramedullary Skeletal Kinetic Distractor (ISKD). It is manufactured by Orthofix, Inc. At present it is on a limited release with only a small number of surgeons trained to use it and of those only a few centers with a large experience with its use. This device can only be used in patients who are skeletally mature and therefore is not applicable in growing children. It is also limited in its ability to correct deformities.

Nevertheless it eliminates all of the problems related to the pins of the external fixator, especially pin site infections, scars and pin site pain. It also reduces the muscle tethering from the pins and makes the physical therapy easier. The ISKD does present some new problems not experienced with external fixator lengthening. There is less control of the lengthening rate and rhythm which can lead to contractures, nerve problems and bone healing problems. In the femur there is a higher rate of premature consolidation while in tibia there is a higher rate of delayed consolidation. Some patients experience severe pain at the onset of lengthening and require an epidural for several days until this pain goes away. All in all however we consider this a major advance. We have performed over 50 such surgeries with good success. None have been for MHE. Deciding between lengthening and shortening is based on a few factors. Shortening is only applicable for discrepancies less than 5cm. Shortening is a much smaller procedure while lengthening is a bigger procedure and longer treatment. Lengthening has a higher complication rate. Shortening cannot correct deformity on the short leg. Lengthening can simultaneously correct deformity and length discrepancy.

Shortening will decrease the patients height by the amount of shortening (max 5cm : 2 inches). Lengthening does not decrease height. Therefore in someone with less than 5cm of LLD and no deformity who is not short or concerned about the height loss, epiphysiodesis or shortening are good alternatives for equalization or LLD. Most cases do have associated deformities and therefore our preference is to perform one operation to simultaneously correct the LLD and the deformity at the same time.

## **Fixator care guide**

### **This surgery involves the application of an external fixator placed into one of the lower limbs of your body.**

When you have your surgery, you will be put under analgesia and feel no pain and when you wake up there will be a lot of people there to help you along the way.

- Your pain control will be managed by a special team of pain specialists. You will have patient controlled analgesia (PCA) where you will be able to adjust your own dose of pain medicine. This is delivered either via an intravenous or epidural catheter. Once taken off (PCA) you will be given oral pain medication to control your pain.
- You will be seen in the hospital by a variety of health care professionals Your Orthopaedic doctor and residents, physician's assistant, medical doctor, nurses, therapists, and a social worker for discharge planning. You will start your training with a physical therapist and learn how to walk and exercise with the fixator. It is important that you put weight on the operated leg (the fixator / frame will protect and support your leg).
- You will start your training with a physical therapist and learn how to walk and exercise with the fixator. It is important that you put weight on the operated leg (the fixator / frame will protect and support your leg).
- Lengthening / Adjustments, Pin Care and Physical Therapy:
  - Begins days after surgery and continues until the length or full correction is achieved. One of the team members will teach you how to do adjustments of the fixator and give you a schedule.
  - Fixator adjustments are typically performed 3-4 times per day All of your dressings will be removed and pin care will be started; you will be taught a pin care routine by the nursing staff:
  - Clean pin sites with a mixture of sterile saline and hydrogen peroxide and dip a sterile cotton tipped applicator into the mixture.
  - Using sterile cotton tipped applicator; you will clean around and away from the skin of each pin.
  - Always when cleaning your pins move away from the skin. Doing otherwise could cause a pin site infection.
  - Use a new cotton tip for each pin site; never use the same cotton tip for more than one pin site as this could cause a pin site infection.
  - Clean each pin site routinely 3 – 4 times per day
  - Wrap white gauze bandage around pin sites. White rolls of gauze bandage are readily available at most drugstores.
  - You will be given prescriptions for pain medications, antibiotics and for physical therapy. You will get a 10 day supply of oral antibiotic to prevent pin infections.

- You can recognize a pin infection by increased pain, redness, drainage of pus, fever, or chills. If you develop a pin infection, call your physician as soon as possible.
- Eat a well balanced diet including protein and calcium to encourage bone growth.
- A Physical Therapist will come to see you and help as well.

Physical therapy sessions: The most important of this task for you during this phase is to follow the schedule and do the exercises your Physical Therapist shows you, this will help prevent joints from getting stiff. While you may need to elevate the leg to prevent swelling, walking and weight-bearing as tolerated is encouraged as prescribed by your doctor.

Physical therapy will help maintain mobility and prevent stiffness of the knee or ankle is done 3 times per week. Physical therapy can be done at a local facility or you may find a physical therapist that makes house calls. Exercises should be done at home as your Physical Therapist prescribes.

You will be followed routinely by the Orthopaedic surgeon that did your fixator surgery and he or she will do follow up X-rays and watch your care. Please let all of your team know if you are in pain as they are there to help you through this process.

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Excerpted from "When Your Child Needs Anesthesia" of the American Society of Anesthesiologists. A copy of this full text can be obtained from ASA, 520 N. Northwest Highway, Park Ridge, Illinois 60068-2573 or ASA website. Please visit the ASA website for more anesthesia information. <http://www.asahq.org>



## **Anesthesia & You...**

### **When Your Child Needs Anesthesia**

A hospital visit can be an anxious time for you and your child. You both will meet many doctors, nurses and other people who will do their best to make your experience a positive one. Just as there are doctors who specialize in different aspects of a child's hospital care such as pediatricians and surgeons, there are doctors called anesthesiologists with special training in the anesthetic care of children.

### **What do anesthesiologists do?**

Anesthesiologists are concerned with many aspects of a child's care. Their main task is to provide safe, optimal conditions during surgery and to make the entire hospital stay as pleasant and comfortable as possible.

Anesthesiologists consider any surgical procedure performed on your child to be of major importance. They are constantly on guard for changes in breathing, heart action, blood pressure or unexpected events which, although rare, may occur during surgery. Apart from assuring the optimal safety of your child during surgery, anesthesiologists are specially trained in how to make the operative procedure as comfortable as possible for your child. Anesthesiologists know how children react to hospitals and surgery. As physicians, they work with other doctors such as pediatricians, surgeons and other specialists to improve the quality of your child's entire hospital stay.

You also may meet anesthesiologists in other hospital areas. For example, if your child needs a specialized radiological test including diagnostic scans, an anesthesiologist may well be present to provide

anesthesia or safe sedation for your child. Following surgery, anesthesiologists are often involved in providing pain relief for your child and are consulted in the pediatric intensive care unit. Even if your child is not undergoing an operation, an anesthesiologist may be consulted for pain management, respiratory care and other medical situations.

### **How can I as a parent help?**

The anesthesiologist and the surgeon will do their best to make your child's visit to the hospital as pleasant as possible; however, you also have a key role to play in your child's care. It is important that you begin preparing your child for the operation as soon as a decision is made to perform surgery. Children tolerate surgery and anesthesia better when they are well-prepared. As with all of us, children have natural fears of the unknown. Anything you can do to relieve these anxieties and to inform your child about the coming events in the hospital and the operating room will greatly improve your child's experience.

Before you explain to your child what to expect, you also must learn what to expect. It is very important to learn about your child's anesthetic experience beforehand by discussing it with the anesthesiologist in the preanesthetic interview.

Once you learn what will happen, you will gain confidence and be better able to talk calmly and honestly to your child. Honesty is a key word. Your child should be told that he or she will be in unfamiliar surroundings but will meet many friendly doctors and nurses. Children need to know that they will have an operation and that there may be some discomfort afterward. Let them know that you may not be with them every minute but will be waiting nearby.

Your composure as a parent is essential. Nothing calms a child more than a confident parent. Although it is natural for parents to have anxiety when their children are having surgery, it is best not to convey this to your child. Talk to your child about what to expect in the hospital such as corridors, hospital beds and the presence of other children. Reassure your child that everything done during the hospital stay will be explained beforehand.

### **What will the anesthesiologist need to know?**

The anesthesiologist will want to make sure that your child is in the best possible physical condition before surgery. You will be asked important questions about your child's general health, including

whether he or she has allergies or asthma, whether there has been any family history of difficulties with anesthesia and what your child's experiences have been with previous anesthetics. During this evaluation, the anesthesiologist will explain the planned anesthetic procedures. The discussion may include whether or not your child will receive anything for sedation before surgery, how the anesthetic will be initiated and maintained, and other pertinent anesthetic details. This is the best time for you and your child to ask questions and express any concerns to the anesthesiologist.

Sometimes minor illnesses such as sniffles and colds may cause problems during some types of surgery and anesthesia. For this reason, the anesthesiologist may feel it is best to postpone surgery. Remember, the anesthesiologist has your child's safety in mind.

### **What if my child has outpatient surgery?**

Outpatient surgery for certain operations has become very common and can be performed without a hospital admission. This means that information about your child needed by the anesthesiologist will be obtained the day of surgery or at some meeting arranged before the day of surgery. Although outpatient or same-day surgery is usually performed for "small" operations, the anesthesia is never "small." It is just as important to follow preoperative directions for outpatient surgery as for operations when your child is brought into the hospital overnight. For example, it is very important for your child's safety to follow closely the anesthesiologist's instructions concerning food and liquid intake.

### **Will my child receive any medication before surgery?**

In the past, virtually every child received an injected sedative before being taken to the operating room. We now realize that many children need less sedation when calm, assured and confident parents help them through the stress of a procedure or hospitalization. In spite of parents' reassurances, however, some children still may require medicine to calm them before surgery. This medication may be given by mouth, injection or rectal suppository. The time before surgery that such premedication is given will vary. The type of medicine used, if any, will be determined by the anesthesiologist during the preoperative visit.

### **How will my child be given anesthesia?**

Anesthetic agents can be started in several ways. Most commonly in adults, anesthesia is started by an intravenous injection so the patient

becomes unconscious rapidly. This is also a method that can be used for children. Another method of beginning anesthesia is to let your child breathe anesthetic agents until losing consciousness. This is called a mask or inhalational induction. With this approach, your child will be asked to breathe through a "space mask" quietly, and no needlesticks will be performed until after your child is sound asleep. The choice of which method to begin anesthesia will be made by the anesthesiologist based on many factors.

Although anesthetics can provide complete pain relief and loss of consciousness during an operation, they do occasionally have side effects. They tend to decrease breathing, heart action and blood pressure. The anesthesiologist is specially trained to ensure that these anesthetic effects are minimized. Different children may awaken from anesthesia at differing rates. Some children may be fully alert upon arriving in the recovery room. Others may be groggy for hours after surgery. If you have any concerns about your child's recovery, you should feel free to ask your anesthesiologist. Although operations are much safer these days, they still produce stress on the body and may cause your child to have a "sick" feeling. Nausea and vomiting are occasional side effects after surgery and anesthesia.

### **What about regional anesthesia for my child?**

In recent years, it has become possible to provide pain relief to specific areas of the body rather than give general anesthesia that causes unconsciousness. For example, if your child is having foot surgery, it is possible to eliminate the feeling of pain in only the foot, either with a local injection of an anesthetic or by regional anesthesia. The most common type of regional anesthesia used in children is called epidural anesthesia. This is very similar to the anesthesia used for childbirth when local anesthesia is injected into the back or tailbone region. Intravenous sedation or inhaled anesthetic agents may be combined with a regional anesthetic. This combination may allow the anesthesiologist to give less general anesthesia. Another advantage is that regional anesthesia is often used to provide pain relief after surgery. Your anesthesiologist can discuss the advantages and disadvantages of regional anesthesia with you.

### **How is pain controlled after surgery?**

The anesthesiologist may be consulted to help manage your child's pain following the surgery. Although "painkilling" injections are still commonly used, other forms of pain management may also be chosen

to provide comfort. For instance, patient-controlled analgesia (PCA) allows a child to self-administer a controlled dose of pain-relieving medicine when needed. A small, computerized pump is programmed by the anesthesiologist, and children 8 years old or older may be instructed on PCA use.

Another approach is the insertion of a tiny epidural catheter in your child's back through which a small dose of medication for pain relief can be given. This allows the child to be more awake and lessens the chance for complications from the use of other pain medications. Sometimes, the epidural pain relief can be continued for several days after the operation.

### **Will I be charged for the anesthesia services?**

The anesthesiologist is a consulting physician who evaluates your child before the operation. Ensures a safe, individualized anesthetic during the entire surgery and provides pain relief following the operation. Like other medical specialists, the anesthesiologist will charge for professional services, and this fee will be separate from the surgeon's fee or hospital's charges. The anesthesiologist's fee reflects the high level of professional care that the anesthesiologist provides for your child during his or her hospital visit.

# **Physical Therapy for Patients with Multiple Hereditary Exostoses**

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## **INTRODUCTION:**

### **What is Physical Therapy?**

Physical therapy is a profession that specializes in the diagnosis and management of movement dysfunction with the goal of restoring, enhancing, maintaining and promoting not only optimal physical function but optimal wellness, fitness and quality of life as it relates to movement and health. (1)

Physical Therapy can only be performed by a licensed Physical Therapist. Physical Therapists possess specialized training at the post-graduate level and have a license to practice Physical Therapy. Many people who have suffered an injury, disease or disability can benefit from Physical Therapy intervention. People who want to prevent illness and disability can benefit from Physical Therapy as well. (1)

### **What does a Physical Therapist do?**

A Physical Therapist performs an examination of many systems in the body. These are the cardiovascular system, the neuromuscular system, the musculoskeletal and the integumentary system. The physical therapist looks specifically at how much a joint can move (range of motion) and how strong the muscles of the body are, including the heart. They look at what activities are hindered by pain or loss of motion or strength. Physical Therapists also examine balance, coordination and walking abilities.

After a complete assessment of the information and an interview with the patient, the Physical Therapist develops a plan of care to address any issues that are present. Based on a patient's personal goals, the Physical Therapist will develop a plan of care with specific interventions to help the patient to achieve those goals. Physical Therapists strive to provide patient and family centered care, which recognizes the importance of the patient and their family in the decision making process.

Physical Therapy interventions can include stretching, strengthening, postural and aerobic exercises, functional activities and activities of daily living training. Physical Therapists also educate patients on the importance of wellness and injury prevention.

Physical Therapists work as a team with other health care professionals including physicians, nurses, social workers, occupational therapists, speech therapists,

recreational therapists, psychologists, and nutritionists.

## **PHYSICAL THERAPY FOR PATIENTS WITH MHE**

### **How can Physical Therapy help patients with MHE?**

For patients with Multiple Hereditary Exostoses, Physical Therapy is very important. The physical therapist works together with the orthopedic surgeon to determine the best course of treatment for exostoses.

#### **Pre-surgery:**

As described throughout this book, exostoses can be present in any bone of the body. Depending on the location and amount of pain and disability, the orthopedic surgeon may or may not recommend surgery. Prior to surgery, the focus of Physical Therapy is to prevent or slow the loss of range of motion and function that can be caused by exostoses. Conservative treatment of exostoses may include physical modalities for pain relief. Although there is no evidence that exostoses growth can be prevented or slowed with Physical Therapy, the disability associated with the exostoses can sometimes be managed effectively with therapeutic interventions. Flexibility and strengthening exercises have been shown to decrease progressive disability in patients with other musculoskeletal disorders like fibromyalgia and rheumatoid arthritis (1, 2, 3).

Another focus of physical therapy, before and after surgery is required, may be to accommodate some of the deformities that occur as a result of the exostoses. These could include shoe lifts to make lengths of the legs equal, splints to protect joints and cushions to make certain positions more comfortable. Equipment can also be provided to make activities of daily living easier and less painful. These include long handled utensils, brushes, reachers and grippers. Problems with mobility can be addressed with walking aides like canes and crutches.

Additionally, it has been shown that cardiovascular exercise can decrease pain and improve overall well being in patients with musculoskeletal impairments (4, 5, 6).

A supervised exercise program that includes aerobic exercise and strength training may also help to decrease the pain and stiffness associated with MHE. While there are many benefits to exercise, anything that causes increased pain in the area of exostoses should be discontinued and reported to the medical professional.

When the decision to have surgery is made, the patient's individual needs after surgery should be anticipated. Often, patients can be seen for a pre-operative Physical Therapy visit. During this visit, patients can learn how to use some of the equipment that they may need to use after the surgery. Practicing these new skills, like walking with crutches, or moving around with a cast or fixator, can make the patient less apprehensive about the rehabilitation process that will take place after the surgery.

This pre-surgery visit is also beneficial to problem solving obstacles to post-surgery rehabilitation. For example, many patients with painful exostoses under their arms may not be able to use traditional axillary crutches to maintain

decreased weight bearing on their legs after surgery. In this case, forearm crutches or a walker may be more appropriate for the patient. Additionally, a patient who does not demonstrate sufficient endurance may need a wheelchair to use for going outside of the house after surgery.

Similarly, the patient who may have decreased weight-bearing abilities after surgery will need to practice new approaches to everyday activities. These might include going up and down stairs, getting into and out of a car, using the toilet, bathing and going to school or work. The patient and the therapist can simulate these activities and problem solve together, before the surgery, so that they are prepared with successful strategies after the surgery is performed.

### **Post-surgery:**

If it is determined that surgery is indicated to remove painful exostoses and increase a patient's function, physical therapy is important following surgery. Depending on the surgery, there may be a period of rehabilitation and the potential for a temporary decrease in function due to pain and muscle weakness. The focus of Physical Therapy after surgery is to minimize the pain and maximize the patient's movement potential around the area that the exostoses were removed.

Some patients with MHE may only require a brief hospital stay after removal of exostoses; others may require a rehab stay where more frequent and intense therapy is required. This depends on the location of the surgery, the extent of the surgery, the amount of function that is lost by the exostoses and the patient's prior level of functioning. During rehabilitation, therapy occurs daily and includes specifically stretching and strengthening of the muscles around the area of surgery. If pain and function were limited prior to the surgery, there may be some soft tissue limitations that are present after the surgery that will require special attention.

Based on the evaluation and orthopedic recommendations, weight bearing will be monitored and progressed as directed. In procedures, which include limb lengthening, physical therapy will also address the joints that surround the fixator to prevent further contractures.

Once surgery incisions are healed, a heated pool may be a good environment for therapy. The water's property of buoyancy can decrease the pain that may occur with weight bearing. Aquatic therapy can also provide an environment where muscles can be strengthened in a fun way with swimming.

Once the patient's goals are achieved and intense physical therapy is not required, transition planning will occur and recommendations for the home, work or school and community will be provided. The development of a home exercise program will maintain the gains that have been achieved through surgery and therapy and prevent secondary complications that are due to pain and immobility.

## **Is Physical Therapy painful?**

Some activities that are performed in Physical Therapy can be uncomfortable because it is hard work. There are things that a therapist can do for their patient to make therapy and exercise more comfortable. Some examples of this are relaxation techniques such as deep breathing and imagery. There are also modalities like heat and ice, which can ease the discomfort caused by exostoses or surgery. Music therapy has been shown to be effective at decreasing pain in patients with other types of chronic pain (7).

## **Are there other diagnoses that are associated with MHE and/ or MHE surgery?**

There are some neurological disorders that can be associated with MHE. These include peripheral neuropathy and Complex Regional Pain Syndrome. (9,10,11) Secondary complications from these can also be addressed with Physical Therapy.

In peripheral neuropathy, the nerves that control the muscles are damaged due to being compressed by exostoses. This leads to a loss of nerve conduction to the muscle and resulting weakness in that muscle. It can affect the motor part of the nerve or the sensory part of the nerve. Impairment can range from slight to complete. Because the nerves are not central to the nervous system, they can regenerate once the compression is relieved surgically. This is, however, a slow process. Physical Therapy can address this with strengthening exercises and bracing, while the nerves to the muscles are healing. (9,10)

Complex Regional Pain Syndrome, type I, (also known as reflex neurovascular or sympathetic dystrophy or reflex sympathetic dystrophy ("RSD")) is a common condition characterized by extreme limb pain associated with autonomic dysfunction. This condition is associated with mild trauma to an extremity, as in the case of a painful exostoses or surgical removal of exostoses.

In this situation, there can be temperature, hypersensitivity, and trophic changes to the effected extremity. Treatment of this disorder in adults ranges from medications, surgical sympathetic nervous system blocks and psychotherapy. In children, studies show the symptoms of this condition can be controlled with physical and occupational therapy.

Treatment for this includes de-sensitization techniques where various textures are applied to the affected area for prolonged periods of time. This usually begins with very light touching with cotton and progresses to different textures, such as cloth and brushes. Weight bearing activities are also essential to retraining the sensory system. Progressing weight bearing to the patient's tolerance is an important part of treatment. If the patient's surgical procedure initially prohibits weight bearing, other activities will have to be improvised in the interim. Exercise is also an integral part of treatment for complex regional pain syndrome and has been shown to be an effective treatment for this chronic pain disorder without the use of medications. (11)

## Is it safe for patients with MHE to participate in sports and recreation?

Fitness and well-being is important for everyone, including the patient with MHE. Every opportunity for continuing exercise in a supervised manner should be encouraged. It may be advisable for schools to provide parents with a detailed physical education curriculum that can be reviewed by the child's orthopedist. Sports and physical education can often be safe to participate in with a doctor's approval as long as the patient is being monitored by the orthopedic surgeon and physical therapist. Non-contact sports like swimming, cycling, dancing, tai chi, yoga and "Pilates" can be safe and fun forms of exercise for some patients with MHE. However, it is important to remember that MHE affects patients differently and specific sports and activities may not be appropriate choices for people whose mobility is blocked by pelvic, hip and leg exostoses. In addition, if a child with MHE experiences pain while participating in sports or PE activities, the child should not be pushed to continue that activity and medical advice should be sought.

Some people with MHE tire very easily when doing physical activity. In addition to blocking certain movements, exostoses put significant pressure on vital structures, causing fatigue. Some children are unable to participate in their school's physical education class. In these cases, there are federal laws under the Americans with Disabilities Act (ADA) and Individuals with Disabilities Education Act (IDEA), which entitle these patients to adaptations and accommodations and prohibit discrimination based on physical disability. Physical Therapists can work with schools to adapt physical education classes or provide alternative activities in order to meet the curriculum's health and physical education requirement. Some families have reported that certain school districts have tried to impose an alternative PE curriculum consisting of a series of written reports on PE-related topics every week. When working with patients suffering from chronic fatigue it is important to remember that this type of extra work, particularly when the child is affected by hand and wrist exostoses, exacerbates fatigue and worsens, rather than remedies, the situation. In some cases where fatigue is severe and participating in PE or complying with standard alternatives are not an option, physical therapy exercises (whether performed at a physical therapy center or as part of a home program), can be used to meet State physical therapy requirements.

Physical Fitness is an individualized concept. There are many types of activities that can be beneficial even if a person with MHE cannot participate in competitive or recreational sports due to fatigue or mobility impairments. Options for fitness include adapted wheelchair sports, seated aerobics and dance, and water aerobics. Physical Therapists can work with patients to determine their optimal activity level and options for fitness and well-being. It is important to remember that the main goal is to have the child function as much as possible in a normal school setting, and that for some students walking to and from classes, sitting through classes, and keeping up with their studies constitutes physical activity.

## CONCLUSION:

An overview of Physical Therapy has been provided; however, each patient is individual and not all Physical Therapy interventions are indicated for all patients. All Physical Therapy should be patient and family centered in its approach. This is very important with MHE, due to the hereditary nature. Exercise and fitness can be a family event and something that they can share to benefit each other.

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# What is Chondrosarcoma?

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The term chondrosarcoma is used to define an heterogeneous group of lesions with diverse features and clinical behavior. Chondrosarcoma is a malignant cancer that results in abnormal bone and cartilage growth. People who have chondrosarcoma have a tumor growth starting from the medullary canal of a long and flat bone. However, in some cases the lesion can occur as an abnormal bony type of bump, which can vary in size and location. Primary chondrosarcoma (or conventional chondrosarcoma) usually develops centrally in a previously normal bone. Secondary chondrosarcoma is a chondrosarcoma arising from a benign precursor such as Exostoses, Osteochondromas or Enchondromas. Although rare, chondrosarcoma is the second most common primary bone cancer.

The malignant cartilage cells begin growing within or on the bone (central chondrosarcoma) or, rarely, secondarily within the cartilaginous cap of a pre-existing Exostoses (peripheral chondrosarcoma).

**Cartilage** is a type of dense connective tissue. It is composed of cells called chondrocytes which are dispersed in a firm gel-like substance, called the matrix. Cartilage is normally found in the joints, the rib cage, the ear, the nose, in the throat and between intervertebral disks. There are three main types of cartilage: hyaline, elastic and fibrocartilage.

It is important to understand the difference between a benign and malignant cartilage tumor.

**Chondrosarcoma is a sarcoma, (i.e.)** a malignant tumor of connective tissue. A chondroma, is the benign counterpart. Benign bone tumors do not spread to other tissues and organs, and are not life threatening. They are generally left alone or cured by surgical removal if they cause symptoms such as tenderness via pressure on surrounding muscles, tendons or nerves.

## Exostoses / Osteochondromas

It is a relatively common lesion and can be solitary or multiple. Multiple osteochondromas occur in multiple hereditary exostosis, usually arise from the metaphysis near the growth plate of long tubular bones. The outer layer of the head of the osteochondroma is composed of benign hyaline cartilage varying in thickness and is delineated peripherally by perichondrium. The cartilage has the appearance of disorganized growth plate and undergoes enchondral ossification with the newly made bone forming the inner portion of the head Exostoses usually

present as slow growing masses, which can be painful if they impinge on a nerve or if the stalk is fractured.

## What are the different kinds of chondrosarcoma?

The single most important factor to consider when evaluating the malignant potential of a chondrosarcoma is its “histologic grade”, determined by the appearance of tumor material under the microscope (Donati et al., 2005; Lee et al., 1999; Marcove et al., 1977; Reith et al., 2003; Springfield et al., 1996; Wang et al., 2001). In addition to histologic grade chondrosarcomas can be classified by their specific histologic variant (clear cell, mesenchymal, dedifferentiated). The lower grade variants of chondrosarcoma can often be quite difficult to differentiate from benign lesions because they have similar appearances on radiographic studies.

Conventional chondrosarcomas are divided into four histologic grades based upon their appearance under a microscope. The grading is based primarily on nuclear size of tumor cells, nuclear staining (hyperchromasia, or darker staining of nuclear material) and cellularity (Evans et al., 1977).

**Grade I (or “low grade”)** tumors most resemble normal cartilage, but may surround areas of lamellar bone (which is not seen in benign lesions), or show atypical cells including binucleate forms (cells with two nuclei instead of one).

**Grade II (or “intermediate grade”)** is more cellular with a greater degree of nuclear atypia, hyperchromasia and nuclear size (Schiller, 1985).

**Grade III (or “high grade”)** tumors have significant areas of marked pleomorphism, large cells with more hyperchromatic nuclei than grade II, occasional giant cells and abundant necrosis. Mitoses are frequently detected.

**The vast majority of chondrosarcoma are Grade I or Grade II. Grade III is rare (Bjornsson et al., 1998).**

**Grade IV.** Belong to this group the subtype variant called mesenchymal and de-differentiated chondrosarcomas. De-differentiated chondrosarcomas, along with mesenchymal chondrosarcomas, are highly malignant, particularly aggressive (i.e., rapidly growing and disturbing surrounding tissues) and carry with them a poor prognosis.

**Hyperchromatic (hyperchromasia)** refers to nuclear material staining more intensely than usual, meaning a more intense cell activity.

**Pleomorphic** means varying shapes between cells of the same type.

**Necrosis** refers to unprogrammed cell death resulting from acute cellular injury. This is in contrast to apoptosis, which refers to programmed cell death.

**Mitoses** indicate cells in the act of replicating.

Chondrosarcomas may also be classified by their histologic sub-type. These sub-types include Clear cell, mesenchymal, and de-differentiated.

**a) Clear cell chondrosarcomas** are low-grade tumors with significant amounts of glycogen. They typically involve the proximal portion of femur, tibia or humerus. Histologically, cells have abundant clear cytoplasm embedded in a loose hyaline cartilaginous matrix and an infiltrative growth pattern. Radiographs show a lytic defect at epiphyseal end of long bones that is sharply demarcated with sclerotic margins. They carry a low recurrence rate and a good prognosis with wide resection.

**Clear cell chondrosarcoma** is different from clear cell sarcoma, which is an aggressive, rare soft-tissue sarcoma that primarily affects the tendons and aponeuroses.

**Clear cell sarcoma** histologically resembles malignant melanoma and rarely affects bones.

**Clear cell chondrosarcomas** produce lytic defects at the ends of long bones and can have the radiographic appearance of **chondroblastoma**, a rare benign cartilage tumor arising in the epiphysis of a long bone in young patients.

**Clear cell chondrosarcomas** frequently extend to joint surfaces.

**b) Mesenchymal chondrosarcomas** are highly aggressive tumors that are radiographically and histologically distinct from conventional and dedifferentiated types. They are eccentrically located in bone and commonly extend into soft tissues. This variant of chondrosarcoma is characterized by a bimorphic pattern that is composed of highly undifferentiated small round cells (similar to Ewing's Sarcoma) and islands of well-differentiated hyaline cartilage. This tumor usually affects young adults and teenagers and shows a widespread distribution in skeleton. The craniofacial bones, the ribs, the ilium and the vertebrae are the most common site (Bertoni et al., 1983). The treatment is radical surgery combined with chemotherapy.

**c) De-differentiated chondrosarcomas** represent about 10% of all chondrosarcomas. The most common sites of involvement are pelvis bones, femur and humerus. This tumor is a distinct variety of chondrosarcoma containing two clearly defined components: a well-differentiated cartilage tumor (enchondroma or chondrosarcoma grade I and II) juxtaposed to a high grade non-cartilaginous sarcoma. The malignant non-cartilaginous component is most frequently malignant fibrous histiocytoma, osteosarcoma or fibrosarcoma, although other malignant tumors have been reported as the differentiated component. Radiographically the tumor produces an ill defined, lytic, intraosseous lesion associated with cortical disruption and extension into the soft tissues. It is more common in adult aged patients and when possible antineoplastic chemotherapy is advised. Surgical treatment has to be radical.

## Who gets chondrosarcoma?

Most chondrosarcomas are low-grade lesions. Low grade means very low attitude to spread out in other organs and tissues. They are typically seen in adults in their late 20s to 60s. They occur more commonly in men than women. Chondrosarcoma is not contagious. It cannot be passed on to another person by exposure to a

chondrosarcoma patient. Although specialists are not yet certain what causes chondrosarcoma, there are several factors that put people at a higher risk. Certain conditions may make people more susceptible to chondrosarcomas:

**a) Enchondromas** are benign tumors of hyaline cartilage, they arise within the medullary cavity, or on the surface of bone, where they are called subperiosteal or juxtacortical chondromas. Enchondromas are the most common of the intraosseous cartilage tumors, they are usually solitary, located in the metaphyseal region of tubular bones.

**b) Ollier's Disease (a.k.a multiple enchondromatosis)** is a disease of multiple benign bone tumors (enchondromas) within the bones which cause affected bones to swell. The disease often primarily affects one side of the body. It is not an inherited disease. Patients have bony swellings, limb shortening and mechanical difficulties, associated with joint disruption and short stature. The condition usually presents before age 10. These typically occur in the bone metaphyses and can lead to secondary deformity of the growth plates. There is a small increased risk of malignant transformation to chondrosarcoma, particularly in flat bones, during adult life.

**c) Maffucci Syndrome** is a rare genetic disorder characterized by benign enlargements of cartilage (enchondromas), bone deformities, and dark, irregularly shaped hemangiomas within the body or on the skin). The disease manifests early in life, usually around the age of 4 or 5 years, with 25% of cases being congenital. There is relatively high risk of malignant transformation to chondrosarcoma in adult life (reportedly 20-30%). Relatively few cases have been published in the English literature.

**d) Multiple Hereditary Exostoses (MHE / MO / HME a.k.a., osteochondromatoses)** is a hereditary skeletal disorder in which there are numerous cartilage-capped excrescences (sp) in areas of actively growing bone (osteochondromas). The condition is genetically heterogeneous, and at least three genes (ext1 and ext2) have been demonstrated to be involved. The reported risk for malignant transformation to chondrosarcoma has been from 2% to 5%. The lesions most at risk for malignant transformation are those occurring near the pelvis, scapula, proximal humerus, proximal femur, and spine. Change in size of the exostosis or onset of pain in an affected adult is cause for further investigation.

People affected by these conditions are at a higher risk because they usually develop several benign bone tumors, which have a higher chance of becoming malignant. People with these hereditary conditions who experience sudden growth spurts or increases in hormone production, such as pregnancy, have a slight increased risk of a benign bone tumor changing into a chondrosarcoma. These patients should be followed by a bone tumor specialist for all of their lives. Skeletal x-rays should be taken in adults every 18-24 months.

## **What is known about the genetics of chondrosarcoma?**

As evolving molecular techniques are available, several genotypic and phenotypic markers for chondrosarcoma have been tested to see if they assist in determining tumor grade prognosis. There is considerable complexity and heterogeneity in the pathologic and clinical behavior of chondrosarcomas. This is reflected in the diversity of cytogenetic and molecular genetic characteristics that have been described in these tumors. Please see Sandberg and Bridge (2003), Sandberg (2004), and Bovee et al. (2005) for a thorough review.

The genetic changes specific to chondrosarcoma continue to be investigated extensively. Although studies have not yet established a specific or recurrent karyotypic feature for any of these tumors, different chondrosarcomas have demonstrated anomalies in several tumor suppressor genes, oncogenes, and transcription factors, including TP53, RAS, EXT1, EXT2, and Sox9. Available cytogenetic and comparative genomic hybridization (CGH) studies reveal changes in some chondrosarcomas, but fail to do so in others. These studies are thus far difficult to interpret.

Based on the available studies, it is likely that chondrosarcomas are generated by a coordinated, multi-step process involving primarily tumor suppressor genes. In fact, the complexity and variety of genetic changes seen in chondrosarcomas may indicate several distinct genetic pathways. Some of the same genes may be involved in each, but the order and manner in which they are affected may differ among chondrosarcomas. Establishing the genes that initiate the neoplastic processes, and that are subsequently involved along the pathways leading to chondrosarcoma may lead to therapies addressing these molecular changes, as has been accomplished for several other sarcomas.

## **Where in the body are chondrosarcomas usually found?**

Chondrosarcomas may develop in any part of the body, but most are commonly found in the pelvis, rib cage, arms (humerus), shoulder blades (scapula) and legs (proximal femur, tibia). Although any bone can be affected, the long bones (legs, arms, fingers, toes,) pelvis and shoulder blades are most commonly involved. Occasionally chondrosarcoma has been found in the spine or skull bones.

It is extremely rare to find chondrosarcoma in any internal organs, but this has been described. If chondrosarcoma spreads from its primary site (i.e., metastasizes), it usually spreads to the lungs. Metastasis is rare with low-grade tumors, but has been seen, even up to 10 years after diagnosis (Lee et al., 1999). About half of grade III and nearly all de-differentiated chondrosarcomas will metastasize.

## **How does someone with chondrosarcoma feel?**

Pain associated with chondrosarcoma is usually in the location of the lesion or adjacent joints, muscles, tendons, nerves, blood vessels, or other soft tissues. In addition to pain, patients with chondrosarcoma may notice an enlargement of a bone or limb, changes in their ability to walk normally, or decreased range of motion in joints near the affected bone. People with benign cartilage tumors (i.e.,

enchondroma or osteochondroma) rarely have pain that is caused by the tumor (Marco et al., 2000b). Most patients with a chondrosarcoma will have pain (Bjornsson et al., 1998; Marco et al., 2000a; Mirra et al., 1985; Murphey et al., 1996) and many will have swelling. It has been reported that in patients with grade I chondrosarcoma, 60% have night pain or rest pain, 21% have vague regional pain, and only 19% have painless tumors (Marco et al., 2000a). Rarely, people will discover they have a chondrosarcoma when they develop a fracture through the tumor (Bjornsson et al., 1998).

Sometimes patients with benign cartilage tumors can have pain caused by something other than the tumor. For example, a rotator cuff injury can be painful at night and an x-ray might show a cartilage tumor in the shoulder. It is very important to determine whether pain is being caused by the tumor or by another process. This difference is vital in the diagnosis and treatment of chondrosarcomas.

## What tests are needed to determine if someone has chondrosarcoma?

After a doctor asks questions (a history) and performs a physical examination, he/she may order plain x-rays to evaluate the area of concern. It can be very difficult for doctors to tell the difference between benign cartilaginous lesions and low-grade chondrosarcomas on x-rays. Both can demonstrate the classic stippled calcified appearance of cartilaginous bony lesions (**Figure 2**). If the hard outside covering of the bone (cortex) appears to be getting chewed away (endosteal scalloping) there is an increased likelihood that the tumor has malignant potential, but is not necessarily confirmatory. Features typical of lower grade lesions include dense calcifications appearing in rings or spicules, uniformly distributed calcifications and eccentric lobular growth of an intramedullary soft tissue mass. One helpful analysis of chondrosarcoma had endosteal scalloping of more than 2/3rd of the cortical thickness, whereas only 9% of enchondromas had similar findings (Murphey et al., 1996).



**Figure 2:** Plain radiographs of a low-grade cartilage lesion in a distal femur bone.

### **CHONDROSARCOMA, PROXIMAL RADIUS (Fig.1:-6:)**

History: 33 y/o male with pain and swelling about elbow.

Findings: Plain films show an expansile lesion. The MR shows cortical destruction and soft tissue extension. Diagnosis: Chondrosarcoma, proximal radius.



Fig. 1: AP

Fig. 2: LAT80B

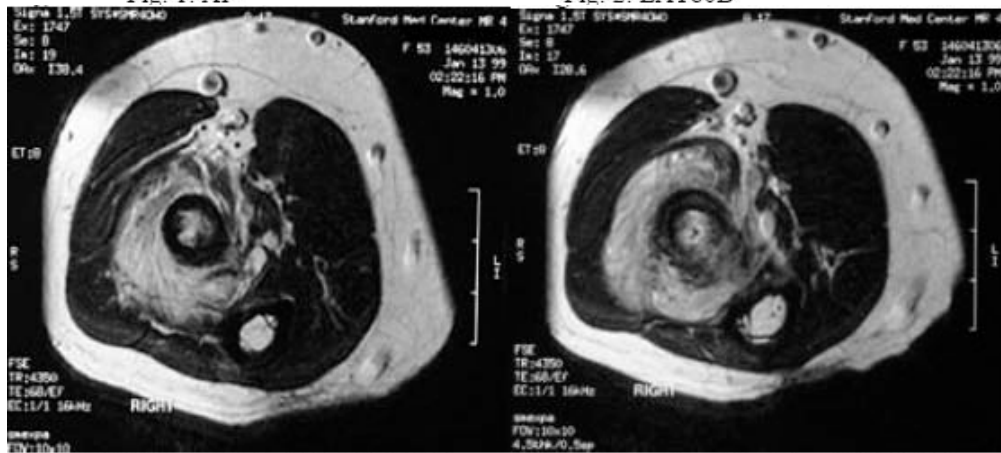


Fig. 3: MR imaging: Axial FSE T2

Fig. 4: MR imaging: Axial FSE T2

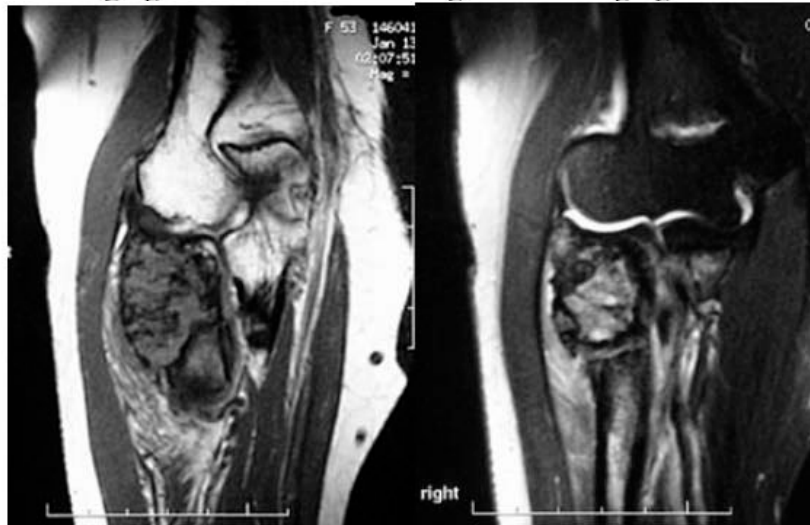


Fig. 5: MR imaging: Coronal T1

Fig. 6: MR imaging: FSE T2

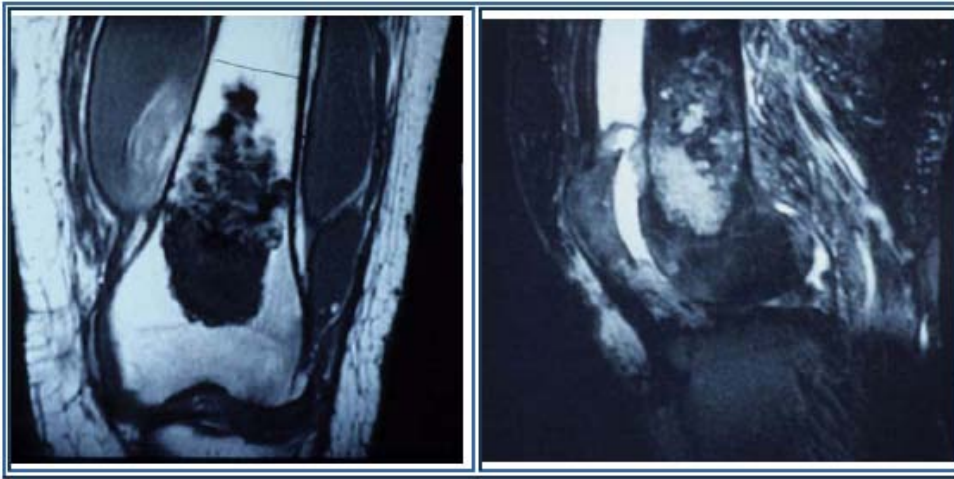
More aggressive (malignant) tumors may show more telling signs of malignancy on x-ray. This includes adaptive changes such as expansion and/or thickening of the cortex and expansion of the surrounding soft tissues (Murphey et al., 1996; Unni, 1996). Findings suggestive of higher grade include faint amorphous calcifications, large areas lacking calcifications and a concentrically growing soft tissue mass.

Perhaps the most reliable radiographic finding when differentiating between benign and malignant lesions is the recognition of change in radiographic appearance over time. In particular, there may be more endosteal scalloping and destruction of the cortex or a decrease in the calcifications with more malignant tumors. If there is no change in the appearance of a benign cartilage tumor on radiographs over time, it is appropriate for the doctor to continue to recommend watchful waiting and repeat x-rays at a later visit.

A bone scan of the entire body can also be helpful in differentiating between benign and malignant tumors, and in identifying whether more than one bone is involved (although multiple bone involvement is rare with chondrosarcomas). This test works by injecting a small amount of radioactive material into the blood stream and taking images using a gamma camera to detect uptake of radioactive material. Lesions demonstrated on bone scan can be compared to internal controls (Murphey et al., 1996). Those lesions demonstrating a higher degree of uptake are more likely to be of higher histologic grade. However, most **Enchondromas** and **Exostoses / Osteochondroma exhibit some radioisotope uptake, and some will erroneously appear as malignancy**. Great caution should therefore be used in drawing conclusions from bone scan results, but these results can add to the overall picture, and better inform the decision making process.



**Figure 3:** Bone scan of patient with left distal femoral chondrosarcoma.



**Figure 4:** MRI images of distal femoral chondrosarcoma.

Recently, there has been some research into the use of a specialized radiographic test called fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET) for grading of tumors in patients with chondrosarcoma (Aoki et al., 1999; Brenner et al., 2004). This test is not yet available at all centers, but may become a useful tool for tumor grading and prediction of outcome in chondrosarcoma patients. This may hence allow for identification of patients at high risk for local relapse or metastatic disease.

**Axial computed tomography (CT)** can assist in determining the extent of bony destruction, and in better delineating bony architecture. CT will also help in better understanding intralesional calcifications. As with plain radiographs, disappearance or change in the nature of calcifications with repeat scanning can be suggestive of malignancy.

**Magnetic Resonance Imaging (MRI)** can be helpful in differentiating between benign and malignant lesions in several ways. First, the degree to which the tumor fills the medullary canal can be helpful (Figure 4). Greater than 90% medullary involvement can be suggestive of chondrosarcoma, while the absence of 90% medullary involvement of non-contiguous areas of cartilage within the bone can suggest the presence of an enchondroma (Colyer et al., 1993). In addition, the timing and progression of gadolinium contrast enhancement patterns may help direct a clinician toward or away from a diagnosis of malignancy (Geirnaerdt et al., 2000). Early enhancement (within 10 seconds of arterial enhancement) may be seen in chondrosarcoma but not in enchondroma. Many surgeons consider MRI critical for surgical planning because it can illustrate the extent of tumor involvement in bone and soft tissues.

### **What if a chondrosarcoma is suspected?**

If chondrosarcoma is suspected, two additional (staging) tests will usually be done to determine whether the tumor has spread. These include: 1) a computerized tomography (CT) scan of the lungs; and, 2) a total body bone scan. The results of these staging studies help physicians determine treatments and outcomes (prognosis). Blood tests are generally not helpful in making the diagnosis,

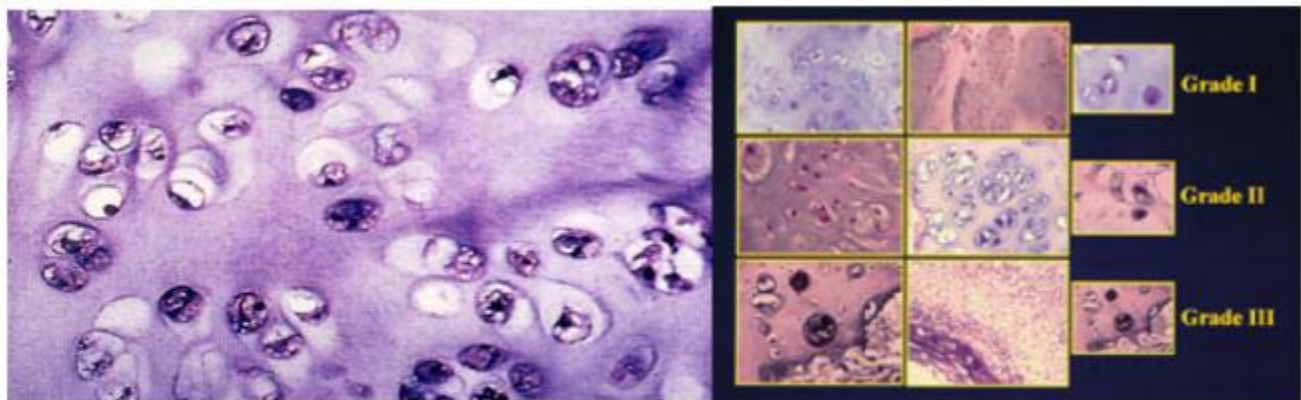
although they can be used to make sure that there is not another process going on, such as infection or a different malignant process. After all of these tests are performed, a sample of the tumor (biopsy) is sometimes necessary to figure out if the problem is truly chondrosarcoma. Most biopsies for chondrosarcoma are achieved by surgical excision (i.e., complete removal of the tumor) of the lesion rather than through incisional biopsy (i.e., surgery to remove only part of the tumor for diagnostic evaluation).

## What will a biopsy tell the patient and the doctor?

When fresh tissue from a chondrosarcoma is viewed under a microscope after a biopsy, it is generally not difficult to identify a clear distinction between normal host tissue and the malignant tissue. However, with higher-grade tumors, more aggressive margins may have more malignant tissue, and have infiltrating satellite components. They will exhibit heterogeneous gross properties including lobulated areas of chalky calcific admixture, regions of firm translucent unmineralized gray cartilage and relatively low vascularity. Higher-grade tumors tend to have areas of necrosis and degenerative material as well (Enneking, 1983).

On microscopic analysis, lower grade chondrosarcomas will exhibit increasing amounts of relatively acellular heavily calcified areas as well as regions of increased activity exhibiting immature cartilage cells with multiple nuclei. By contrast, higher-grade lesions tend to harbor regions of densely packed hyperchromatic malignant looking cells

(**Figure 5**). There may sometimes be difficulty in determining that these cells are truly of cartilaginous origin. In some regions, myxomatous changes, and highly degenerative areas may make identification impossible.



**Figure 5:** Grade II chondrosarcoma: Increased cellularity and atypical cells.

As both benign and malignant cartilage lesions can share certain clinical and histological characteristics, pathologists will often consider the patient's history when interpreting specimens. Permeation of cortical and/or medullary bone is an important characteristic of conventional chondrosarcoma that the pathologist can use to separate it from **Enchondroma / Osteochondroma**. The decision by the orthopaedic oncologist for definitive treatment is based upon the areas of

highest concern for malignancy. Lesions appearing more aggressive clinically and radiographically must be widely resected without biopsy to avoid contamination of healthy tissue, which would likely necessitate an additional surgery. However, this remains controversial. The surgeon decision is based on history and progression of the lesion referred by the patients and confirmed by the previous examinations. The histological grade is sometimes necessary to plan a preoperative chemotherapy in IV grade chondrosarcomas. Or on the other hand to plan a more conservative surgery in border line lesions (benign, low-grade)

## What are the current treatments for chondrosarcoma?

For benign-appearing, asymptomatic cartilage tumors (i.e., enchondroma), patients are usually followed with clinical evaluation and sequential x-rays 3, 6 and then 12 months apart. This is continued unless there is a change in clinical examination findings or the radiographic appearance of the lesion at different points in time. Symptomatic enchondromas as well as exostoses /osteochondroma (i.e., those that cause pain, discomfort, or are disfiguring but do not show indications of malignancy) can be treated with a relatively non-invasive procedure. Enchondromas can be curetted out from inside the medullary canal of the bone with placement of a bone graft, while exostoses can be excised from the bone surface. Fractures through the tumor (**called a pathologic fracture**) can be treated with either concurrent or staged treatment of both the fracture and the lesion if there is concern over the risk of recurrent pathologic fracture.

Surgical resection remains the primary and most successful means of treating chondrosarcomas. The decision regarding the extent of surgical resection and adjuvant therapy is dependent upon the clinical and histologic characteristics of the lesion. Optimal treatment for low-grade chondrosarcoma remains a dilemma for surgical oncologists, but no chemotherapy or radiation is indicated. For higher-grade tumors, with a worse prognosis for recurrence and metastasis, adjuvant therapies may be considered.

Table 1	TUMOR	SYMPTOMS	PROGNOSIS	TREATMENT
BENIGN	<b>Enchondroma</b> <b>Osteochondroma</b>	Usually no symptoms	Excellent	Surveillance, intralesional excision if symptomatic
MALIGNANT (Low grade)	<b>Grade I</b> <b>Chondrosarcoma</b>	60% are painful	Excellent	Controversial: Extended intralesional excision vs. Wide resection
MALIGNANT (low grade)	<b>Grade II</b> <b>Chondrosarcoma</b>	Up to 80% painful	Good	Wide resection
MALIGNANT (Intermediate grade)	<b>Grade III</b> <b>Chondrosarcoma</b>	Up to 80% painful	Fair	Wide resection. Chemotherapy and radiation therapy in select cases
MALIGNANT (High grade)	<b>De-differentiated</b> <b>Chondrosarcoma</b>	Most are painful	Poor	Wide resection. Chemotherapy when possible in all cases Radiation therapy in selected
MALIGNANT (High grade)	<b>Mesenchymal</b> <b>Chondrosarcoma</b>	Pain and swelling	Fair-Poor	Wide resection. Chemotherapy in all cases

Irradiation may be useful in younger patients or those with metastatic disease, where surgery would cause major unacceptable morbidity or be technically impossible (Krochak et al., 1983). This remains controversial. Cytotoxic chemotherapy is ineffective against traditional chondrosarcomas, but may have a role in the dedifferentiated subtype or in stage IV disease (Dickey et al., 2004). There are no established regimens for such cases. For patients who have developed pulmonary metastatic disease, treatment in a clinical trial at a Sarcoma center, or with conventional chemotherapy, if appropriate for the patient, may be indicated. Proton beam radiation is generally reserved for refractory tumors in high risk anatomic areas such as the skull base and axial skeleton. As these adjunctive modalities are of no proven benefit, the burden of a cure still falls upon adequate initial surgical resection.

In the past, wide resection was considered the method of choice for all chondrosarcomas. Unfortunately, these tumors are frequently found in regions such as the pelvis or proximal long bones, where aggressive surgical management may endanger adjacent vital organs and structures or compromise limb function. Thus, less aggressive approaches such as marginal excision and extended intralesional excision with margin expansion using adjuncts such as phenol or cryotherapy have received increasing attention with a national study underway to investigate efficacy. Most surgical oncologists prefer limb salvage techniques with bone graft and prosthetics, preserving the function of the limb. Amputation is still used in advanced disease or as a last option.

**Phenol** is an organic compound sometimes used as an adjunct to surgical excision of chondrosarcoma to destroy any remaining diseased tissue. **Cryotherapy**, using liquid nitrogen, is often used as an adjunct to surgical excision of chondrosarcoma to destroy remaining diseased tissue.

While rigorous evidence-based criteria are presently lacking, individual centers may have their own criteria and algorithms for surgical decision-making. In general, benign lesions should be treated conservatively, while high-grade malignancies should be treated aggressively with complete resection. If surgical margins are not clear on histologic evaluation of the tissue after resection of an intermediate- or high-grade lesion, wider surgical resection and possibly bone and/or joint prosthesis may be necessary.

### Clinical Trials

Optimal treatment for low-grade chondrosarcoma remains a dilemma for surgical oncologists. For patients who have developed pulmonary metastatic disease, treatment in a clinical trial at a Sarcoma center, or with conventional chemotherapy, if appropriate for the patient, may be indicated. At the time of this writing, there is a multi-center, international trial evaluating the diagnosis and treatment of low grade chondrosarcoma and a trial dealing with advanced chondrosarcomas sponsored by the National Institutes of Health, the Southwest Oncology Group, and The American College of Surgeons Oncology Group, Sarcoma Alliance for Research Through Collaboration (SARC), Patient Advocacy Groups

## Where is the best place to go to receive appropriate treatment?

Patients with chondrosarcoma are best treated at major Sarcoma centers with specialized diagnostic and treatment facilities and the availability of Musculoskeletal Tumor Specialists or Orthopedic Oncologists. Because this, like many other bone cancers, are not common, it is often a good idea to seek an opinion from a major cancer center that has a wide experience in treating bone cancers. A major sarcoma center will offer an organized group of doctors and other health care professionals who work together to provide the best treatment options and recovery. If your primary care physician suspects chondrosarcoma, a simple referral to an orthopedic doctor may not be adequate. Be sure that you are referred to an orthopaedic oncologist or "bone cancer specialist."

## What are the chances for cure and survival from chondrosarcoma?

In general, the prognosis for chondrosarcoma depends on the grade of the tumor and the attainment of complete excision of the tumor and other conditions the patient has such as diabetes, lupus, and clotting and coagulation problems. For lower grade chondrosarcomas, prognosis is very good after adequate excision. There is a low incidence of pulmonary metastasis if the primary lesion is widely resected. Metastasis to other bones can occur, but is much less common. Dedifferentiated chondrosarcoma have a uniformly poor prognosis.

**Table 2:** Survival Features of Chondrosarcoma

(Table 2).	Five-year Survival	Metastatic Potential	Recurrence rate
Grade I	90%	0%	Low
Grade II	81%	10-15%	Fair
Grade III	29%	>50%	High
Dedifferentiated	<10% (1-year)	Most	High

## Summary

Cartilaginous lesions of the human skeleton exist on a continuum spanning from the completely benign embryonic inclusion, to the dangerously aggressive neoplastic process. In order to determine the appropriate treatment for each individual lesion, musculoskeletal oncologists must take into account the clinical, radiographic and histologic characteristics of the tumor.

It is important for patients to seek treatment for these tumors at a Sarcoma center with availability of specialists possessing a sound understanding of these lesions and a firm grasp of the evolving treatment options. The health care team at these centers will keep patients informed about the details of the treatment course in both the short and long term. Understanding and recognizing the spectrum of appearances of the various types of chondrosarcoma allow improved patient assessment and are vital for optimal clinical management including diagnosis, biopsy, staging, treatment and prognosis. As more advanced molecular

tools for predicting tumor behavior are developed, more sophisticated means of diagnosing and treating these tumors will be developed and put into use.

Musculoskeletal Tumor Society is a good resource to find a musculoskeletal oncologists. <http://msts.org/find.html>

The MHE Research Foundation website also has listing of Sarcoma centers

## **In 2002 the World Health Organization (WHO) has redefined the definition of Multiple Hereditary Exostoses (MHE) into Multiple Osteochondromas (MO) (Bovee and Hogendoorn, 2002).**

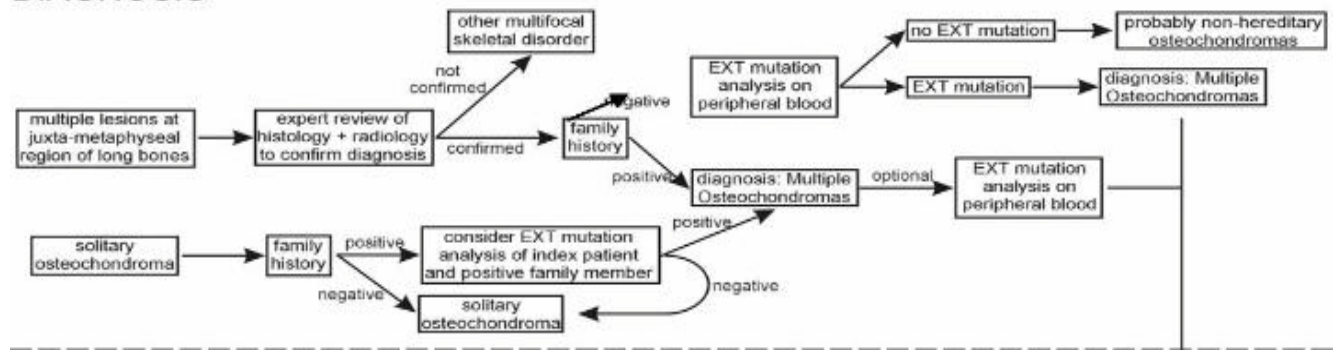
Pancras C.W. Hogendoorn, MD, PhD, Professor of Pathology, Department of Pathology, Leiden University Medical Center, Molecular tumor pathology and tumor genetics, Netherlands. Head of EuroBoneT consortium, a European Commission granted Network of Excellence for studying the pathology and genetics of bone tumors, Principle Researcher MHERF research registry.

This was done because of the very wide and a-specific use both inside the medical community as well as by patients of the term "exostosis". It ranges in use from osteochondroma (Khurana et al., 2002), the benign cartilage tumor involved in MHE, to a perversion in the direction of growth (eg Nora's lesion or Trevor disease) and even to a reactive process (eg subungual exostosis). Therefore the WHO decided to redefine the terminology for the bony outgrowths into different terms reflecting the different nature of the diseases involved aiming at a better defined diagnosis. "Exostoses" involved in MHE are now specified as osteochondromas and defined as benign cartilaginous tumors.

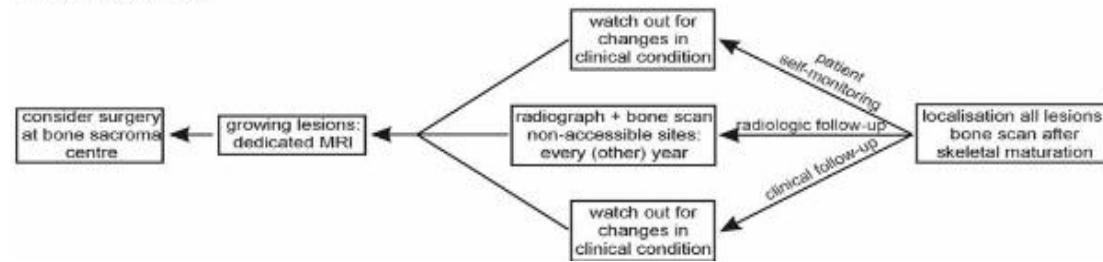
The current WHO definition of an osteochondroma is "a cartilage capped bony projection arising on the external surface of bone containing a marrow cavity that is continuous with that of the underlying bone" (WHO 2002) (Khurana et al., 2002). With this change in terminology, Multiple Hereditary Exostoses is no longer applicable as name for this disorder. That is why the WHO also changed the name of MHE to Multiple Osteochondromas (MO) and stated that: "A diagnosis of multiple exostoses can be made when radiologically at least two osteochondromas of the juxta-epiphyseal region of long bones are observed. MO is diagnosed in case of a positive family history and/or a proven germline mutation in one of the EXT genes" (WHO 2002) (Bovee and Hogendoorn, 2002).

It is very important to correctly diagnosis Multiple Osteochondromas. Especially good monitoring of the patient is important after Multiple Osteochondromas is established. This scheme was taken from "Multiple Osteochondromas: clinicopathological and genetic spectrum and suggestions for clinical management." by L. Hameetman, J.V.M.G. Bovee, A.H.M. Taminiau, H.M. Kroon and P.C.W. Hogendoorn published Hereditary Cancer in Clinical Practice (Volume 2(4) pp. 161-173) (Hameetman et al., 2004).

## DIAGNOSIS



## FOLLOW-UP



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# **The Genetics of Multiple Hereditary Exostoses**

## **A Simplified Explanation**

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**There is an accompanying video presentation on the  
MHE Research Foundation website**

## **Multiple Hereditary Exostoses - General aspects**

### **Introduction**

Multiple Hereditary Exostoses (MHE), also often referred to as Hereditary Multiple Exostoses (HME), is a bone disorder that affects mainly the long bones. Recently the term Multiple Osteochondroma (MO) was suggested by the World Health Organization (WHO) as the preferred term to refer to this disorder and throughout this article both abbreviations MHE / MO / HME will be used. MHE / MO / is characterized by the presence of bony protuberances, which are described as osteochondromas or exostoses. They are located mainly near the joints and are often accompanied by skeletal deformities.

MHE / MO / HME was first described in the year 1786, while the name multiple exostoses was first proposed in 1876. In the literature one can find many other names describing this disorder; such as diaphyseal aclasis, chondral osteoma, osteochondromata, multiple cartilaginous exostoses, (multiple) exostosis, deforming chondreodysplasia, osteogenic disease, etc.

Single osteochondromas or exostoses are very common in the general human population (1 to 2%) but the incidence of multiple osteochondroma is estimated to be 1 in 50,000. However, isolated communities have been described where a much larger fraction of the population is affected. MHE / MO / HME is not a unique human disease, as osteochondromas have been found in many species including cats, dogs, sheep, horses, lizards, lions, etc. A large osteochondroma was even found on the bones of a dinosaur.

### **Clinical aspects**

MHE / MO/ HME is a condition a person is born with and osteochondromas can be present at birth but in most patients they are noticed within the first six years of life. By the age of 12, almost all patients have been diagnosed. Most affected bones are the femur, tibia and fibula, but this is very variable from patient to patient. In theory every bone which is formed by endochondral bone formation (a process of bone formation in which cartilage is formed first, which then is replaced

by bone) can be affected. Facial bones remain normally unaffected. MHE / MO / HME is characterized by great variation in number, size, location and shape of the osteochondromas, even within a family. The osteochondromas continue to grow until closure of the growth plates at the end of puberty. Development of new osteochondromas or further growth at later age is not common but has been described. In addition to the presence of the bony outgrowths, skeletal deformities such as bowing and shortening of the forearm, knee, hip and ankle deformities can be present. Mild short stature is also observed in many patients.

Many complications have been observed in MHE / MO / HME patients, including compression of tendons, nerves, muscles, ligaments and spinal cord. The pressure of the osteochondromas on neighboring tissues and organs causes often almost permanent pain. The most serious complication is the development of a malignant tumor (a chondrosarcoma) out of an osteochondroma, mostly occurring at adult age. This event is observed in 1 to 5% of the cases and is often preceded by abnormal growth of the osteochondroma or changes in the cartilage cap which covers the osteochondroma. The only known treatments for MHE / MO / HME are surgical removal of the osteochondromas, (which often grow back at the original site) and surgical procedures to correct bone deformities and limb length discrepancies. Surgery, physical therapy and pain management are currently the only options available to MHE / MO / HME patients, and their success varies from patient to patient and many struggle with pain, fatigue and mobility problems throughout their lives. At present there is no definite cure for MHE / MO / HME.

In addition to MO/MHE, two syndromes have been described where multiple exostoses are one of the symptoms: the Langer-Giedion syndrome (LGS) and the Proximal 11p deletion syndrome (P11pDS). Patients suffering from LGS have multiple osteochondromas, but also show typical characteristic features such as a bulbous nose, protruding ears, sparse hair, cone-shaped epiphyses and often mental retardation. Patients with P11pDS syndrome (also called Potocki-Shaffer syndrome) have multiple osteochondromas, skull defects and often mental retardation.

## Genetic aspects

MHE / MO / HME is an autosomal dominant hereditary disorder. This means that a patient with MHE / MO / HME has a 50% chance of transmitting the disorder to his/her children, so he/she has a 50% chance that his/her child will also have MHE / MO / HME and 50% that this is not the case. This is equal for both male and female patients. Normally the disorder does not skip a generation. So if one of the parents does have MHE / MO / HME and the child does not, this child will normally only have unaffected children. However, some patients have very mild symptoms so it may only look like they are unaffected. In this case, their children are still at 50% risk of developing MHE / MO / HME. This may create a situation where it seems that the disorder skips a generation. In such cases, genetic analysis may reveal the true status. In a large number of patients there is no previous family history of MHE / MO / HME and both parents are unaffected. In these patients a new mutation has occurred. These patients have then again a 50% risk of transmitting the disorder to their children.

To understand why MHE / MO / HME is an autosomal dominant disorder one has to understand the basic principles of heredity. All our genetic information, which determines a great deal of the development of our body, lies within our DNA. This DNA is organized in chromosomes, which are numbered from 1 to 22 while the sex determining chromosomes are named X and Y. At the moment of conception, the egg cell which comes from the mother fuses with the sperm cell, which is provided by the father. The egg cell contains 23 chromosomes (chromosome 1 to 22 and an X chromosome) and the sperm cell contains 23 chromosomes (1 to 22 and an X or Y chromosome). After fertilization, a fertilized egg with 46 chromosomes is formed from which an embryo and eventually a human being will develop.

During this process the cells will divide with duplication of the DNA. Therefore, in the human body (almost) every cell (with the exception of the egg and sperm cells) contains the 46 chromosomes containing the entire DNA content. Males have one X and one Y chromosome, females have two X chromosomes. Certain parts of our DNA, the so-called genes, contain all the information necessary to make proteins. Every gene is located on a certain chromosome. If such gene contains an error, which is called a mutation, this can affect the formation and/ or function of this gene and thus the function of the corresponding protein. Loss of altered function of this protein can then result in a visible defect or disorder.

At present we know that there are two such genes, the EXT1 gene on chromosome 8 and the EXT2 gene located on chromosome 11, which are important with respect to MHE / MO / HME. If a mutation in one of these two genes occurs, this inactivates this gene and/or the corresponding EXT1 or EXT2 protein. Therefore, MHE / MO / HME patients have only one functional EXT1 or EXT2 gene, so have only half of the functional EXT1 or EXT2 proteins compared to people without a mutation in EXT1 or EXT2. Both EXT1 and EXT2 have a function in cartilage and bone development and it appears that the remaining EXT proteins are not enough for normal bone development. The fact that MHE / MO / HME patients still have one functional EXT gene (and EXT protein) is not enough and therefore the effect of the mutation is dominant. This is in contrast with the so-called recessive diseases, such as, for example, cystic fibrosis (CF) where you only develop the disease if you have a mutation in both genes. People with a mutation in only one of their CF genes do not get CF but are only carriers of the disease. The chance for two parents who are both carriers of having an affected child is in this case 25%.

Approximately 60 to 70 % of MHE / MO / HME patients have a mutation in the EXT1 gene and 20 to 30% have an EXT2 mutation. In 10 to 20% of the patients, no mutation is found. This can be explained by the presence of a yet unknown, additional EXT-causing gene or by the fact that not all mutations can be detected by the techniques commonly used in DNA diagnostics for MHE / MO / HME. The fact that most of the families have a different mutation makes genetic analysis for MHE / MO / HME very laborious and expensive, and it is therefore only performed in a few laboratories worldwide. At present, the outcome of genetic testing has no effect on determining orthopaedic care but genetic testing may give more options in making choices in reproduction. Once the mutation is identified in one patient, testing of family members is relatively easy and it can confirm their affected/non-

affected status. Moreover, presymptomatic and prenatal diagnostics through chorionic villus sampling (CVS) at 10-12 weeks gestation or amniocentesis at 16-18 weeks gestation is available and also preimplantation diagnostics (PGD) can be offered to those families for whom the disease-causing mutation has been identified.

At present, it is still not very clear whether the differences in severity of the disease are related to whether the patient has an EXT1 or EXT2 mutation. There seems to be a tendency that EXT1 mutations cause a more severe type of MHE / MO / HME, but this needs to be confirmed in larger studies. In addition, there is no explanation for the variation in severity that is observed between patients within one family, thus with the same mutation. It is therefore at present impossible to make predictions with regard to severity of the condition based upon mutation type.

## Concluding remarks

Although still many questions remain unanswered, many aspects of MHE / MO / HME have been elucidated in the past years. The increasing understanding of the genetic and biological aspects of this disorder will increase the quality of the (genetic) counseling of MHE / MO / HME patients, which should always be offered when a diagnosis of MHE / MO / HME is made.

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# The Genetics of Hereditary Multiple Exostoses

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## Introduction

Hereditary multiple exostosis (HME) is a skeletal disorder characterized by the presence of numerous bony outgrowths (osteochondromas or exostoses) that develop next to the growth plates of all the long bones (Solomon 1963). The most striking clinical feature of HME is the numerous cartilage-capped exostoses, which are associated with the entire skeleton. Skeletal surveys suggest that a solitary exostosis can be found in 1-2% of the general population (Mirra 1989). A diagnosis of HME is made in individuals where the presence of multiple exostoses has been noted on clinical and/or radiologic examination. The average age at identification of a first exostosis is three to four years with 96% of individuals with HME developing exostoses by the age of 12 (Schmale et al. 1994; Wicklund et al. 1995).

In addition to having exostoses, individuals with HME can have other skeletal and non-skeletal complications. Skeletal complications include limb discrepancy and bony deformities such as bowed radius, conical ulna, and valgus deformity of the hip and ankle (Solomon 1963; Karasick et al. 1997; Vanhoenacker et al. 2001).

Mild short stature is also a characteristic feature of the condition with the mean height being  $170 \pm 7.9$  cm for males and  $155 \pm 6.9$  cm for females (Wicklund et al. 1995). The presence of exostoses can lead to a number of non-skeletal complications such as compression of tendons, muscles, ligaments, blood vessels, and nerves, all of which can cause pain. Blood vessel involvement has been found in 11.3% of individuals with HME, while peripheral nerve compression and spinal cord compression have been found in 22.6% and 0.6% of individuals with HME, respectively (Wicklund et al. 1995). A recent study focusing on pain in HME found that 84% of individuals report having pain as a result of having HME (Darilek et al. 2004). By far the most severe complication of HME is the malignant transformation of an exostosis into a chondrosarcoma. Recent studies estimate the lifetime risk of malignant degeneration to be about 2-4% for individuals with HME (Schmale et al. 1994; Wicklund et al. 1995; Darilek et al. 2004). Many individuals with HME undergo surgery as a result of having HME-related complications. Studies have shown the 66-74% of individuals with HME undergo at least one operation for their exostoses, with the average number of surgeries being two to three (Schmale et al. 1994; Wicklund et al. 1995).

## Inheritance

HME is an autosomal dominant condition with a penetrance ranging from 96 to 100% (Schmale et al. 1994; Wicklund et al. 1995). Estimates of the prevalence of HME have ranged from 0.9 in 100,000 in a European population to 100 in 100,000 in a small, closed population of the Chamorros of Guam (Voutsinas and Wynne-Davies 1983; Krooth and Cunningham 1986; Hennekam 1991). A more recent

study in the state of Washington found the prevalence to be at least one in 50,000 however, this is thought to be an underestimate as more mildly affected individuals do not come to medical attention (Schmale et al. 1994). Most people with HME have a family history of the condition. Solomon (1963) reported that 66% of individuals with HME have a family history while more recent studies have increased this estimate to 70-90% (Schmale et al. 1994; Wicklund et al. 1995)

## Gene Linkage

Linkage studies were conducted to locate the gene or genes leading to HME. It was long suspected that a gene for HME would map to the Langer-Giedion region on chromosome 8. Langer-Giedion syndrome is a rare, autosomal dominant disorder in which individuals have multiple exostoses, characteristic facial features, and cone-shaped epiphyses and are frequently mentally retarded (OMIM #150230). The exostoses found in HME and Langer-Giedion syndrome are indistinguishable. In addition, a patient with HME and a balanced chromosomal translocation involving chromosomes 8 and 11 had been described, adding to the evidence for the presence of an HME gene on chromosome 8 (Ogle et al. 1991). In order to determine if a gene for HME was indeed located on chromosome 8, Cook et al. in 1993 conducted linkage analysis on eleven multigenerational families with HME. They found significant evidence for linkage of a disease locus to the Langer-Giedion region on chromosome 8 for 70% of the families studied. This finding also indicated that HME is a genetically heterogeneous disorder, having at least one other locus somewhere else in the genome. In 1994, Wu et al. studied two large, multigenerational families with HME, for which linkage to chromosome 8 was excluded, in order to try to localize other genetic loci for HME. They performed a genome-wide search and found evidence for a second locus for HME on chromosome 11. Linkage to a third locus on chromosome 19 was also reported by Le Merrer et al. in 1994. In 1996, the linkage to chromosomes 8 and 11 was confirmed by Blanton et al. and in 2001 linkage analysis conducted by Francannet et al. confirmed that there are at least three EXT loci, with 69% of their families showing linkage to EXT1 on chromosome 8, 21% to EXT2 on chromosome 11, and 3% to EXT3 on chromosome 19 (Blanton et al. 1996; Francannet et al. 2001). These findings suggested that these three loci account for over 90% of cases of HME, but that at least one additional HME locus might exist. However, neither the EXT3 gene nor any additional EXT genes have been cloned and these finding have not been confirmed in other studies.

## Genes

Of the three genes linked to HME, two have been cloned: EXT1 on chromosome 8q23-q24 and EXT2 on chromosome 11p11-p12. Homologous genes have been found in mice, *Caenorhabditis elegans*, *Drosophila*, and *Xenopus* (Lin and Wells

1997), Stickens et al. 1997, (Bellaiche et al. 1998; Katada et al. 2002)]. EXT1 and EXT2 are large genes. EXT1 is made up of eleven exons spanning over 250 kilobases while EXT2 contains fourteen exons and is spread over a region of more than 100 kilobases (Ludecke et al. 1997). The genes code for ubiquitously expressed proteins of 746 (EXT1) and 718 (EXT2) amino acids and share approximately 70% similarity at the amino acid level (Ahn et al. 1995; Wuyts et al. 1996). Both the EXT1 and EXT2 proteins have been found to localize predominately to the endoplasmic reticulum but function in the Golgi apparatus as hetero-oligomers to synthesize heparan sulfate chains (Lin and Wells 1997; McCormick et al. 1998; McCormick et al. 2000). Normally functioning EXT1 and EXT2 proteins are required for proper bone growth. Since both proteins play a role in the development of benign bone tumors and there is an increased risk for individuals with HME to develop chondrosarcoma, it is thought that the EXT genes function as tumor suppressors. This role has been supported by loss of heterozygosity (LOH) studies that have revealed that both the EXT1 region on chromosome 8 and the EXT2 region on chromosome 11 show LOH in HME-related and isolated chondrosarcomas (Hecht et al. 1995; Raskind et al. 1995; Hecht et al. 1997).

Mutations Research has shown that approximately 64-76% of families with HME have a mutation in the EXT1 gene and approximately 21-30% have a mutation in the EXT2 gene (Dobson-Stone et al. 2000; Wuyts and Van Hul 2000; Francannet et al. 2001). Currently, 66 different mutations have been found in the EXT1 gene and 31 different mutations have been found in the EXT2 gene. The EXT1 mutations include thirteen nonsense mutations, twelve missense mutations, and four splice sites mutations as well as 37 mutations that consist of small insertions or deletions. The majority of the EXT1 mutations have been found to cause premature termination of the EXT1 protein. While most of the mutations reported are private mutations, two mutations, 1469delT and C1018T, have been reported in nine and ten unrelated patients, respectively (Wuyts and Van Hul 2000; Francannet et al. 2001). The distribution of the mutations over the EXT1 gene has been analyzed and reveals that while mutations occur throughout the entire length of the gene, most of the mutations are distributed over the first six exons of the gene with the last five exons, which contain a conserved carboxyterminal region, having significantly fewer mutations (Wuyts and Van Hul 2000). The EXT2 gene has been shown to have a comparable spectrum of mutations. Eleven of the 31 reported mutations are nonsense mutations while four are missense mutations, three are splice site mutations, and thirteen are frameshift mutations (Wuyts and Van Hul 2000; Francannet et al. 2001). As in EXT1, most of the mutations are private mutations that are distributed over the first eight exons of the gene, again leaving the carboxyterminal region with fewer mutations than one would expect with a random distribution (Wuyts and Van Hul 2000). The majority of the EXT mutations are expected to cause premature termination of the EXT proteins

leading to loss of function of the proteins (Francannet et al. 2001). A multi-step model was proposed to describe the development of an exostosis but there is little experimental data to support this model. Only heterozygous mutations have been identified in the vast majority of exostosis samples with only a few exostosis samples demonstrating multiple mutations or LOH (Hall et al. 2002).

## Genotype-Phenotype Correlations

In 2001, Francannet et al. conducted a clinical survey and mutation analysis for 42 families with HME, consisting of 217 affected individuals, in order to determine whether there is any correlation between HME phenotype and genotype. They divided the families into two groups based on the phenotypic expression of the disease. The first group, referred to as group S, included families with severely affected members while the second group (group M) included families whose members had a moderate HME phenotype. They also further divided group S into four subgroups labeling them as type IS to IVS, with IVS being the most severely affected group overall. Of the 42 families studied, seven belonged to group M and 35 to group S. Of the group S families, 10 were labeled type IS, five type IIS, eight type IIIS, and two type IVS. Most of the families with a moderate phenotype (group M) were found to have EXT2 mutations, while all of the type IIS, IIIS, and IVS families except one were found to have EXT1 mutations. The more severe HME phenotype (type S) was significantly associated with EXT1 mutations while a more moderate phenotype was associated with EXT2 mutations. Of note, chondrosarcomas were only found in patients with EXT1 mutations. The only correlation found between phenotype and location of mutation in the EXT genes was found in the IVS group (most severe phenotype). Mutations associated with this group of patients were consistently located in the first exon of EXT1.

Phenotypic variability has also been noted in HME. In this study, 2/3 of families with an EXT1 mutation were noted to exhibit phenotypic variability, while in all but two families with EXT2 mutations members showed a homogeneous phenotype (Francannet et al. 2001). Novel EXT1 and EXT2 mutations identified by DHPLC in Italian patients with multiple osteochondromas. (Luca Sangiorgi 2005 Sep;26(3):280. PMID: 16088908) Mutation Screening of EXT1 and EXT2 by Denaturing High-Performance Liquid Chromatography, Direct Sequencing Analysis, Fluorescence in Situ Hybridization, and a New Multiplex Ligation-Dependent Probe Amplification Probe Set in Patients with Multiple Osteochondromas (Wim Wuyts 2008 Jan;10(1):85-92. PMID: 18165274)

This genotype-phenotype analysis suggests that more severe HME phenotypes presenting with large number of exostoses, short stature, and/or vertebral exostoses are more commonly found in individuals with an EXT1 mutation. One concern about the study is the criteria used for categorizing phenotype severity. The researchers used five factors to judge severity: age at onset (severe if less

than or equal to 3 years), number of exostoses at time of evaluation (severe if greater than or equal to 10), location of exostoses (severe if vertebral exostoses noted), stature (severe if less than or equal to the tenth percentile), and functional rating (severe if the rating was "fair"). For an individual's phenotype to be labeled severe, three or more of these factors had to be rated severe. The authors do not explain why these specific cutoffs are determined. There currently is no consensus as to what constitutes a severe versus a moderate HME phenotype and thus severity ratings can be extremely subjective. Of note, the genotype-phenotype correlations were based on family phenotype, not on individual phenotype, and a family's phenotype was based solely on the degree of severity of the most affected members. As a result, a family with a number of mildly or moderately affected members could have been labeled as severe if a few of the members are found to have severe phenotypes. This can lead to a bias, as only those most severely affected family members are considered when making genotype-phenotype correlations. In addition, it is not clear whether the study population is made up of individuals ascertained from a clinic population or from the general population of individuals with HME. If the study population is a clinic population, it is possible that only more severely affected individuals and families were studied, again biasing the study toward a more severe phenotype by not including those individuals and families who never come to medical attention due to being mildly affected by HME. In order to determine whether genotype-phenotype correlations can be made in HME, additional studies should be carefully undertaken and consider disease severity by individual.

## Genetic Counseling and Genetic Testing

Most individuals with HME have a parent who also has the condition, however, approximately 10% of individuals with HME have the condition as a result of a de novo mutation and are thus the first person in their family to be affected (Schmale et al. 1994). Individuals with HME have a 50% chance of having an affected child.

Genetic testing for HME is available on a clinical basis. Testing consists of sequence analysis of the entire coding regions of both the EXT1 and EXT2 genes. The mutation detection rate has been found to be approximately 70%, as sequencing of the coding regions of the genes may not identify all mutations (Philippe et al. 1997; Raskind et al. 1998). If a mutation is not detected by sequence analysis, fluorescent in situ hybridization (FISH) analysis can be used to detect deletions in the EXT1 and EXT2 genes. Prenatal diagnosis through chorionic villus sampling (CVS) at 10-12 weeks gestation or amniocentesis at 14-18 weeks gestation as well as preimplantation genetic diagnosis (PGD) is available for individuals for whom genetic testing has identified a disease-causing mutation.

Though genetic testing is available for HME, the severity of the condition cannot be predicted based on mutation type. In fact, the severity of the condition varies even within members of the same family. Genetic counseling is indicated for

individuals and families with HME to aid them in understanding information about HME and making decisions based on this information.

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## **Genetic Testing and Reproduction**

### **Authored by the MHE Research Foundation**

Most individuals with MHE / MO / HME have a parent who also has this condition however approximately 10% of individuals with MHE / MO / HME have this condition as a result of a spontaneous mutation are thus the first person in their family to be affected. There are two known genes that cause this disease EXT1 located on chromosome 8q23-q24 and EXT2 located on chromosome 11p11-p12. Approximately 60 to 70 % are located EXT1 gene and 20 to 30% are located EXT2 mutation. In 10 to 20% of the patients, no mutation is found. Offspring of an affected individuals have a 50% risk of inheriting the altered gene for hereditary multiple exostoses / Multiple Osteochondroma.

### **Prenatal diagnosis:**

You must have genetic testing preformed and your MHE / MO / HME mutation (disease-causing allele) must be found before prenatal diagnosis can be preformed. Analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

**Preimplantation genetic diagnosis (PGD)** is a test that screens for genetic mutations among embryos created during invitro fertilization. Screening Embryos for Disease: Note You must have genetic testing preformed and your MHE / MO / HME mutation (disease-causing allele) must be found before PGD can be preformed.

Developed in the early 1990's, preimplantation genetic diagnosis (PGD) is a way for couples to prevent a pregnancy affected by a genetic condition disorder. This form of genetic testing is performed on embryos during an in vitro fertilization (IVF) cycle. The embryos that have been analyzed and are found to be normal are transferred into the woman's uterus, where, hopefully, they will implant and result in the birth of a healthy child. With PGD, DNA samples from embryos created in-vitro by the combination of a mother's egg and a father's sperm are analyzed for gene abnormalities that can cause disorders. Fertility specialists can use the results of this analysis to select only mutation-free embryos for implantation into the mother's uterus.

Before PGD, couples at higher risks for conceiving a child with a particular disorder would have to initiate the pregnancy and then undergo chorionic villus sampling in the first trimester or amniocentesis in the second trimester to test the fetus for the

presence of disease. If the fetus tested positive for the disorder, the couple would be faced with the dilemma of whether or not to terminate the pregnancy.

If you are considering PGD, you should research as many fertility centers as possible and ask for their success rates. Success rate can vary, consider asking the success rate using PGD for single gene disorders and ages of these woman. You may also want to inquire how long the fertility center has been performing PGD.

**Genetic Testing of the EXT1 and EXT2 genes is available on a clinical basis**  
Please read, Genetic Guides

	Laboratory below offering each gene test	Laboratory below offering each gene test	Laboratory below offering each gene test	Laboratory below offering each gene test
<u>PCR-direct sequencing (polymerase chain reaction)</u>	<u>Department of Medical Genetics, University of Antwerp Belgium</u>	<u>The Genetic Unit ,The Rizzoli Orthopaedic Institute, Bologna, Italy</u>	<u>GENDIA (for Genetic diagnostics) Belgium</u>	<u>GeneDx Laboratory USA</u>
<u>(DHPLC) denaturing high performance liquid chromatography</u>	<u>Department of Medical Genetics, University of Antwerp Belgium</u>	<u>The Genetic Unit ,The Rizzoli Orthopaedic Institute, Bologna, Italy</u>	<u>GENDIA (for Genetic diagnostics) Belgium offered as research</u>	
<u>(MLPA) multiplex ligation-dependent probe amplification</u>	<u>Department of Medical Genetics, University of Antwerp Belgium</u>	<u>The Genetic Unit ,The Rizzoli Orthopaedic Institute, Bologna, Italy</u>	<u>GENDIA (for Genetic diagnostics) Belgium offer as research</u>	
<u>(FISH) Fluorescence In Situ Hybridization</u>	<u>Department of Medical Genetics, University of Antwerp Belgium</u>	<u>The Genetic Unit ,The Rizzoli Orthopaedic Institute, Bologna, Italy</u>		
<u>linkage analysis</u>	<u>Department of Medical Genetics, University of Antwerp Belgium</u>	<u>The Genetic Unit ,The Rizzoli Orthopaedic Institute, Bologna, Italy</u>		
<u>Fertility centers offering PGD. All centers doing PGD will do set up they may need the link for GENDIA</u>			<u>PGD set up for use in GENDIA (for Genetic diagnostics) Belgium</u>	
<u>Prenatal diagnosis</u>	<u>Department of Medical Genetics, University of Antwerp Belgium</u>	<u>The Genetic Unit ,The Rizzoli Orthopaedic Institute, Bologna, Italy</u>		<u>GeneDx Laboratory USA</u>

## The MHE / MO / HME Guide

### Learning about your child's special needs and how you as a parent can help with your child's Education.

#### Authored by The MHE Research Foundation

The issues MHE / MO / HME parents face trying to help cover their child's educational needs and let the school, teachers and all staff know about the needs of their children can be over whelming. Children with special needs many times require what is called an Individualized Education Plan (IEP) as well as a letter from the parent. U.S. Department of Education *A Guide to the Individualized Education Program PDF guide book link is located on the MHE Research Foundation website*

The affects MHE / MO / HME can vary from child to child it is important to keep in mind not all the issues listed will necessarily happen to your child, but if they do you will have this information and other information located on our website to help guide you along the way. Children with MHE / MO / HME have challenges they will need to overcome in school they can have mobility issues, pain issues, sleep issues, fatigue issues, social issues and may miss a larger number of days from school than other children that do not suffer from MHE / MO / HME, all can affect your child's education. It also has been reported some children may also have learning issues, sensory issues there is research being conducted on these issues now.

You also need to remember that children with MHE / MO / HME are subject to the same educational issues as children that do not suffer from MHE / MO / HME. Sometimes learning disabilities can be over looked.

Before your child is enrolled or returns to school, write a letter directed to the school, teacher and all staff that will be in contact with your child explaining your child suffers from MHE / MO / HME and has disabilities as a result.

You can print some of the materials located on our website and given them to the school along with the letter you write to your child's school team. Remember that your child in not only dealing with one classroom teacher and school nurse in the lower grades, but other staff in the school as well. In the higher grades the challenges become even larger as children start to change classes and have a larger number of children to deal with throughout the day. So make sure that everyone is on the same page and knows your child's special needs can become more difficult.

When writing important letters to the school make sure you address your letter to all staff that will be dealing with your child.

The first paragraph could read your child is suffering from a condition called

Multiple Hereditary Exostoses or Multiple Osteochondroma. MHE / MO / HME is a genetic bone disorder in which multiple benign cartilage-capped bone tumors that outward from the long bones, growth plates or from the surface of flat bones throughout the body. These Exostoses / Osteochondromas can cause numerous problems, including: compression of peripheral nerves or blood vessels; irritation of tendons and muscles resulting in pain and loss of motion; skeletal deformity; short stature; limb length discrepancy; chronic pain and fatigue; mobility issues. Describe where and how MHE has affected your child and write please see the attached Clinical Information Guides . If you child already has an IEP make copies of this as well.

Close your letter by saying how you look forward to working with the school staff in the upcoming school year.

Signature

Your contact information

We also suggest that you can make this a tear of letter, this way all school staff that receive a copy of your the letter you are writing can mail or hand back that they have received and have read the information you have supplied the school. You can also attach a self addressed envelope with stamp.

Example

-----Tear of and return-----

Teacher or school staff name: \_\_\_\_\_

I have read the letter and information in enclosed sent by Your NAME concerning Your Child's Name.

Teacher or school staff signature: \_\_\_\_\_

Date: \_\_\_\_\_

You will need to write a letter to the school requesting an IEP for your child. Provide expectations and concerns regarding your child's school performance in a organized and concrete manner. Expect all language in the IEP to be clear, understandable. Ask what you can do to reinforce your child's school program and instruction at home, during holiday and summer breaks.

**MHE / MO / HME School Needs Check List, this check list has been put into a PDF file linked on the MHE Research Foundation website.**

*(PDF form can be directly typed into and saved or filled out by hand, the check list contains the bullet information below with boxes you can simply check off.)* This PDF file is also use full when given to the medical professionals who are caring for your child as well. This assists the medical professional to see some of the issues your child is facing.

## School Needs Check List.

- Make sure to inform the school when surgery is planed and also if possible
- ▶ surgeries that you may know could be required in the future, like a fixator surgery the following year for example.
- ▶ Will your child need to be home schooled due to surgery?  
It may take time for your child to get up and moving in the morning, so if
- ▶ your child is slow in the morning let the school know about this and the other issues below
- ▶ Your child may need to bath or shower to loosen up in the morning
- ▶ Your child may have a hard trouble getting fully dress by him/she self putting on shoes and socks, clothing with buttons
- ▶ Does your child have pain at times though out the day?
- ▶ Does your child need to take pain medication during school?
- ▶ Your child may use need to crutches, a walker, cane, or wheelchair all the time or from time to time
- ▶ Does your child have issues walking to school or the school bus stop?
- ▶ Does your child have issues getting on and off the school bus?
- ▶ Does your child need special transportation provided by the school?

## Activities in School:

You can request in writing for an Occupational therapy (OT) evaluation for your child to be preformed. Many of the issues below are addressed during Occupational therapy, where the school has an Occupational therapist work with your child during school hours. You can also request a Physical therapy (PT) as well. In many states, if the school cannot provide the service needed in the school itself the department of education will pay for these sessions with an OT or PT therapist that they have contracted with. You can also

- ▶ request Assistive technology evaluation and after this evaluation if your child need in the lower grades an AlphaSmart (small light weight key board to take note and type small paragraphs the screen is very small on the AlphaSmart and only show a few lines of text types) For older children laptops can be ordered. Learning to type software as well as word prediction and voice activated software can be ordered for lap tops. These computers can be taken home with the child. If an AlphaSmart or Laptop is ordered make sure the class room has a printer as well.

- ▶ Does your child have issues with stairs in school?
- ▶ Does your child need use the elevator at school?
- ▶ Does your child need help use the bathroom by him/she self due to buttons on clothing at school?
- ▶ Does your child need help to carry lunch tray?
- ▶ Does your child need help opening my milk carton?
- ▶ Could your child be embarrassed to speak up concerning problems your child is having in school with the teacher or school nurse?
- ▶ Does your child may get tired at school and want to rest? and is there a location to rest?

- ▶ Does your child tend to get fatigued during the school day?
- ▶ Does your child have a hard time raising my hand in class because of his/her MHE?
- ▶ Does your child need a second set of books (one to stay at school and one for home)?
- ▶ Has your child's Orthopaedic physician given you guide lines on the amount of weight your child backpack can weigh?
- ▶ Does your need a set of notes of class work due to writing issues?
- ▶ Does your child need to get up and walk around in the classroom because of stiffness or pain?
- ▶ Does your child need extended time for exams/tests?
- ▶ Does your child need a scribe, answer recorded in any manner written into his/her IEP
- ▶ Would it help your child to take exams/testing at a different location, so they could get up if they needed to move because they are stiff?
- ▶ Would you like a Para - Professional to be assigned to your child or class room if needed?

## PE/Gym:

- ▶ Does your child have trouble sitting cross-legged/Indian style, running, jumping, hopping, skipping, bending, pulling, hanging, pushing, kicking, throwing, tumbling?
- ▶ Can your child play soccer, basketball, volleyball or contact sports?
- ▶ Has your Orthopaedic physician given any restrictions to participate regular gym activities?
- ▶ Could your child have issues with getting undressed for gym in front of other kids because of my scars or the appearance of their bone or exostoses/osteochondromas.

## After School hours:

- ▶ Does your child need to take a nap or rest period after school?
- ▶ Does your child need amount of homework modified to insure that your child completes homework given?
- ▶ Be sure to keep records of the number of days missed from school and why and also the number of days your child maybe need to come home early.

**Other warning flags to watch out for and bring up to the teacher and during your IEP meeting.**

## Attention:

- ▶ Fails to pay close attention to details or makes careless mistakes in schoolwork, work, or other activities
- ▶ Has difficulty sustaining attention in work tasks or play activities
- ▶ Does not follow through on instructions and/or fails to finish schoolwork, chores
- ▶ Has difficulty organizing tasks and activities
- ▶ Avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort such as homework and organizing work tasks
- ▶ Loses things consistently that are necessary for tasks/activities ( i.e., toys, school

assignments, pencils, books, or tools)

- ▶ Is easily distracted by outside influences
- ▶ Is forgetful in daily/routine activities

## Other

- ▶ Confuses left and right
- ▶ has a poor sense of direction; slow to learn the way around a new place; easily lost, confused or has fear in unfamiliar surroundings
- ▶ Is slow to learn new games and master puzzles
- ▶ Performs inconsistently on tasks from one day to the next
- ▶ Has difficulty generalizing (applying) skills from one situation to another

## Comprehension:

- ▶ Not interested in listening to stories, audio tapes, songs and a variety of listening activities
- ▶ Experiences difficulty distinguishing between similar sounds
- ▶ Experiences difficulty following directions, especially when it's more than one at a time
- ▶ Doesn't enjoy participating in class discussions and rarely raises his/her hand to respond
- ▶ Slow to follow oral discussion and take notes

## Oral Language:

- ▶ Weak articulation skills
- ▶ Difficulty with oral language uses lots of interjections and hesitations (umm, uh, well...)
- ▶ Weak verbal expression
- ▶ Grammar skills are quite weak
- ▶ Forgets a lot of words and can't often remember what he/she was going to say
- ▶ Weak vocabulary

## Reading:

- ▶ Confuses words and letters
- ▶ Has difficulty recognizing and remembering sight words
- ▶ Confuses similar-looking words (i.e., beard/bread)
- ▶ Demonstrates poor memory for printed words
- ▶ Often loses place when reading, requires finger tracking
- ▶ Difficulty when silent reading, needs to mouth words or whisper when reading
- ▶ Doesn't enjoy reading
- ▶ Reluctant Reader
- ▶ Reading is slow and deliberate
- ▶ Lots of word substitutions, omissions and invented words
- ▶ Cannot skim or scan for pertinent information

- ▶ Has poor retention of new vocabulary
- ▶ Cannot re-tell parts of the story, prediction skills are weak

## Written Work:

- ▶ Rarely enjoys writing and responds negatively to written activities
- ▶ Written work is rarely legible, writing is messy and incomplete, with many cross outs and erasures
- ▶ Experiences difficulty when copying instructions from the board, orally or chart paper
- ▶ Rarely completes written assignments
- ▶ Written work is poorly organized and difficult to follow
- ▶ Punctuation and grammar is weak and often missing
- ▶ Lots of word substitutions, omissions and invented words
- ▶ Written ideas lack cohesion and sequence
- ▶ Ideas are poorly written and expressed
- ▶ Written work is often difficult to understand
- ▶ Spelling is weak, Spells poorly and inconsistently (i.e., the same word appears differently other places in the same document)
- ▶ Letters and/or words are often reversed
- ▶ Demonstrates delays in learning to copy and write
- ▶ Uses uneven spacing between letters and words, and has trouble staying 'on the line'
- ▶ Copies inaccurately (i.e., confuses similar-looking letters and numbers)
- ▶ See Occupational therapy (OT) evaluation and Assistive technology evaluation information above

## Mathematics:

- ▶ Has trouble learning multiplication tables and rules
- ▶ Rarely sequences numbers, equations and formulas appropriately
- ▶ Has trouble telling time
- ▶ Has trouble conceptualizing the passage of time
- ▶ Poorly aligns numbers resulting in computation errors
- ▶ Has difficulty with learning and memorizing basic addition and subtraction facts
- ▶ Difficulty mastering number knowledge(i.e. Recognition of quantities without counting)
- ▶ Has difficulty with comparisons (i.e., less than, greater than)
- ▶ Has difficulty estimating quantity (i.e., quantity, value)
- ▶ Unable to perform 'mental math'
- ▶ Has trouble interpreting graphs and charts
- ▶ Computations are usually inaccurate
- ▶ Many careless errors, often chooses the wrong operation
- ▶ Difficulty understanding mathematical concepts
- ▶ Rarely uses mathematical terms appropriately both orally and in written work
- ▶ Does not remember the math facts (although today, many children aren't committing the math facts to memory)
- ▶ Cannot do mathematical word problems

## Motor Skills:

- ▶ Is often clumsy and accident prone
- ▶ Has limited success with games and activities that demand eye-hand coordination
- ▶ Has weak co-ordination
- ▶ Awkward gait
- ▶ Weak fine motor skills (evidenced in art, written work, copying, writing on the chalkboard etc.)
- ▶ Holds pencils, pens, crayons, scissors inappropriately - too hard, due to exostoses/osteochondroma
- ▶ Also trouble with buttons, hooks, snaps, zippers and trouble learning to tie shoes
- ▶ Exhibits weak large motor co-ordination during gym and recess (falls or trips frequently)
- ▶ Experiences difficulty using small objects or items that demand precision (i.e., Legos, puzzle pieces, tweezers, scissors)

## Social Skills:

- ▶ Has a difficult time establishing friends or has friends that are younger
- ▶ Rarely accepted by peers (kids could be being teased)
- ▶ Has difficulty 'joining in' and maintaining positive social status in a peer group
- ▶ Argues with peers
- ▶ Doesn't accept responsibility well
- ▶ Has trouble knowing how to share/express feelings
- ▶ Has trouble 'getting to the point' (i.e., gets bogged down in details in conversation)
- ▶ Avoids peer contact and is often ridiculed or involved in ridiculing
- ▶ Demands instant gratification, seeks a great deal of attention
- ▶ Doesn't like to follow rules or routines or does not like when routines are broken
- ▶ Prone to tantrums
- ▶ With drawn
- ▶ Takes issues with large numbers of people, example lunch room or play ground
- ▶ Has a hard time picking up facial expressions, bodily gestures, tone of voice, etc...example your child think a person is upset with them and they are not or takes common experiences that most people take in stride out of context.
- ▶ Has trouble setting realistic social goals

## Behavior Skills:

- ▶ Often is hyperactive
- ▶ Rarely completes tasks in the allotted time
- ▶ Often acts out in the classroom and doesn't follow routines and rules
- ▶ Can be extremely moody and acts impulsively
- ▶ Very disorganized or over organized

- ▶ Inattentive and distractible
- ▶ Rarely thinks before acting
- ▶ Does not get along well with peers
- ▶ Decision making skills are weak and is often late or absent
- ▶ Easily Frustrated
- ▶ Anxiety

## Other Sensory issues:

- ▶ Touch/Texture, feeling of certain clothing on skin, clothes feel scratchy or itchy, children could not tolerate the roughness  
Food texture, Easily gags due to texture or tastes. A "picky" eater or crunchy texture may be loved, while any other texture is rejected or groups: sweet, sour, bitter or salty. Sometimes a child may only eat foods from one of these categories
- ▶ Loud noise examples music, movies, play ground, lunch room, parades, parties, fireworks

## Evaluation requests

- ▶ IEP evaluation
- ▶ Learning disability evaluation
- ▶ Occupational therapy (OT) evaluation
- ▶ Physical therapy (PT) evaluation
- ▶ Assistive technology evaluation

## Preparing for Your Next Medical Appointment

Whether the patient is your child or yourself, you are an important part of a health-care team. Together with the orthopaedist treating you and/or your child, your team may also include physical therapists, occupational therapists, pharmacists, pain specialists, x-ray technicians and others involved with the ongoing treatment of MHE / MO / HME. During a doctor's appointment, it's easy to get sidetracked. Anxiety often runs high and can block your clearest thinking. Doctors have schedules to keep and are often pressed for time. If you feel pressured during the appointment, it may be difficult to stay focused on addressing each of your concerns. Maximize your time with the doctor by preparing for your appointments beforehand. Here are a few suggestions for making the most of your next appointment.

☒ Fill out the Clinical information form. You can call the doctor's office and have these forms mailed to you before your medical appointment.

☒ If seeing a new doctor, or if you are having several problems that need to be addressed, tell the office when you call for an appointment that you will need sufficient time to talk to the doctor.

☒ If you or your child is a new patient, arrange to have medical records and x-rays transferred to the new physician before the appointment.

☒ Write down your questions and then prioritize them. For instance, put a #1 by the most important, a #2 by the next most important, etc.

☒ Start by asking the doctor the most important question first, then the next most important, and so on. Stay focused on your questions. If you wander into interesting side stories you will lose valuable time.

☒ When you arrive for the appointment, give the medical assistant a copy of your written questions and ask that they be put on the front of the chart so the doctor can see them.

☒ If possible, have someone come with you into the exam room. This person should also have a copy of the questions. He or she can take notes during the appointment and help make sure your questions have been addressed to your satisfaction.

☒ Bring all your medications with you to the appointment. Let your doctor know all the over-the-counter medications you are taking and how much.

☒ If you hear words you do not understand, ask for an explanation. Doctors are used to using medical terms and sometimes forget that it includes words the rest of us do not understand.

☒ If the doctor does not have enough time, ask if someone else on his / her staff can answer your questions. Remember, you have a right to have your questions answered.

☒ When a surgery is recommended, ask about the benefits and the risks, as well as any alternatives. Ask your doctor about pain management after surgery, as well as pain management after release from the hospital.

☒ Ask your doctor to show you the X-rays and have him/her explain the surgery showing you the X-rays. This way you can show the doctor pointing to the X-ray something you may not understand.

☒ Don't be afraid to let your doctor know you don't understand something.

☒ Spend time after the visit talking with the person who came with you. He or she will likely have good insights about the appointment and can help you identify any areas that are still unclear.

☒ Ask the doctor to send a copy of his /her report to your home.

☒ Pain Issues can be better addressed by your doctor if you provide complete background information: If you have pain issues, you will want to fill out a pain diary. Make a copy of your pain diary to give to your doctor, so you can go over it together and the copy will be made part of your medical records.

Include the following information:

• Location(s) of your pain.

• Description of your pain: sharp, stabbing, burning, nagging, stiff, throbbing, etc.

• It's helpful to also use a pain scale to describe your pain: 0 being the least amount of pain and 10 being the most amount of pain.

• How long does the pain last?

• How do you feel when you wake up?

• What aggravates the pain?

• When does pain start in the day?

• What activities cause pain?

• What is pain like at mid-day; what is pain like in the evening; what is pain like at night in bed.

- Does pain wake you up?
- Do you currently take medication for pain. If so, what do you take (name of drug, dosage)
- Are there any other treatments that help relieve your pain (i.e. heat, ice, exercise, rest, etc.)
- How long does it take to get pain relief after you take your medication?
- Does pain come back before you are next scheduled to take your medication?
- Does driving affect your pain?
- What activities are you unable to do because of pain?
- How does your job (or school) affect your condition?

# Multiple Hereditary Exostoses

## MHE / MO / HME

### CLINICAL INFORMATION FORM

Name: \_\_\_\_\_

Address: \_\_\_\_\_

Phone number: \_\_\_\_\_ Email: \_\_\_\_\_

Your Signature: \_\_\_\_\_ Date: \_\_\_\_\_

- Height: \_\_\_\_\_ Weight \_\_\_\_\_ • Age of diagnoses of MHE / MO / HME: \_\_\_\_\_
- Age of first Surgery \_\_\_\_\_ • Age of last surgery \_\_\_\_\_ • Number of surgeries you have had \_\_\_\_\_
- Do you have a family history of MHE / MO / HME ? Yes ☐ or No ☐

<b>Site</b> <u>Hand</u> Yes <input type="checkbox"/> or No <input type="checkbox"/> Surgery Yes <input type="checkbox"/> or No <input type="checkbox"/> Number of surgeries _____ Age _____	<b>Site</b> <u>Elbow</u> Yes <input type="checkbox"/> or No <input type="checkbox"/> Surgery Yes <input type="checkbox"/> or No <input type="checkbox"/> Number of surgeries _____ Age _____	<b>Site</b> <u>Knee</u> Yes <input type="checkbox"/> or No <input type="checkbox"/> Surgery Yes <input type="checkbox"/> or No <input type="checkbox"/> Number of surgeries _____ Age _____
<b>Site</b> <u>Forearm</u> Yes <input type="checkbox"/> or No <input type="checkbox"/> Surgery Yes <input type="checkbox"/> or No <input type="checkbox"/> Number of surgeries _____ Age _____	<b>Site</b> <u>Wrist</u> Yes <input type="checkbox"/> or No <input type="checkbox"/> Surgery Yes <input type="checkbox"/> or No <input type="checkbox"/> Number of surgeries _____ Age _____	<b>Site</b> <u>Ankle</u> Yes <input type="checkbox"/> or No <input type="checkbox"/> Surgery Yes <input type="checkbox"/> or No <input type="checkbox"/> Number of surgeries _____ Age _____
<b>Site</b> <u>Scapula</u> Yes <input type="checkbox"/> or No <input type="checkbox"/> Surgery Yes <input type="checkbox"/> or No <input type="checkbox"/> Number of surgeries _____ Age _____	<b>Site</b> <u>Shoulder</u> Yes <input type="checkbox"/> or No <input type="checkbox"/> Surgery Yes <input type="checkbox"/> or No <input type="checkbox"/> Number of surgeries _____ Age _____	<b>Site</b> <u>Foot</u> Yes <input type="checkbox"/> or No <input type="checkbox"/> Surgery Yes <input type="checkbox"/> or No <input type="checkbox"/> Number of surgeries _____ Age _____
<b>Site</b> <u>Pelvis and Hip</u> Yes <input type="checkbox"/> or No <input type="checkbox"/> Surgery Yes <input type="checkbox"/> or No <input type="checkbox"/> Number of surgeries _____ Age _____	<b>Site</b> <u>Lumbar Spine</u> Yes <input type="checkbox"/> or No <input type="checkbox"/> Surgery Yes <input type="checkbox"/> or No <input type="checkbox"/> Number of surgeries _____ Age: _____	<b>Site</b> <u>Cervical Spine</u> Yes <input type="checkbox"/> or No <input type="checkbox"/> Surgery Yes <input type="checkbox"/> or No <input type="checkbox"/> Number of surgeries _____ Age _____
<b>Site</b> <u>Ribs</u> Yes <input type="checkbox"/> or No <input type="checkbox"/> Surgery Yes <input type="checkbox"/> or No <input type="checkbox"/> Number of surgeries _____ Age _____	<b>Site</b> <u>Fingers</u> Yes <input type="checkbox"/> or No <input type="checkbox"/> Surgery Yes <input type="checkbox"/> or No <input type="checkbox"/> Number of surgeries _____ Age _____	<b>Site</b> <u>Toes</u> Yes <input type="checkbox"/> or No <input type="checkbox"/> Surgery Yes <input type="checkbox"/> or No <input type="checkbox"/> Number of surgeries _____ Age _____

- Have you ever developed a chondrosarcoma? Yes ☐ or No ☐ yes at age: \_\_\_\_\_ location: \_\_\_\_\_



## **Management of Chronic Pain**

### **Authored by the MHE Research Foundation**

Making the journey from patient to person takes time. The isolation and fear that can overwhelm a person with chronic pain grows over time. And the return to a fuller, more rewarding life also takes time.

#### **► Keep a pain Diary**

#### **► Accept the Pain**

Learn all you can about your physical condition. Understand that there may be no current cure and accept that you will need to deal with the fact of pain in your life.

#### **► Get Involved**

Take an active role in your own recovery. Follow your doctor's advice and ask what you can do to move from a passive role into one of partnership in your own health care.

#### **► Learn to Set Priorities**

Look beyond your pain to the things that are important in your life. List the things that you would like to do. Setting priorities can help you find a starting point to lead you back into a more active life.

#### **► Set Realistic Goals**

We all walk before we run. Set goals that are within your power to accomplish or break a larger goal down into manageable steps. And take time to enjoy your successes.

#### **► Know Your Basic Rights**

We all have basic rights. Among these is the right to be treated with respect, to say no without guilt, to do less than humanly possible, to make mistakes, and to not need to justify your decisions, with words or pain.

#### **► Recognize Emotions**

Our bodies and minds are one. Emotions directly affect physical well being. By acknowledging and dealing with your feelings, you can reduce stress and decrease the pain you feel.

#### **► Learn to Relax**

Pain increases in times of stress. Relaxation exercises are one way of reclaiming control of your body. Deep breathing, visualization, and other relaxation techniques can help you to better manage the pain you live with.

#### **► Exercise**

Most people with chronic pain fear exercise. But unused muscles feel more pain than toned flexible ones. With your doctor, identify a modest exercise program that you can do safely. As you build strength, your pain can decrease. You'll feel better about yourself, too.

## **See the Total Picture**

As you learn to set priorities, reach goals, assert your basic rights, deal with your feelings, relax, and regain control of your body, you will see that pain does not need to be the center of your life.

You can choose to focus on your abilities, not your disabilities. You will grow stronger in your belief that you can live a normal life in spite of chronic pain.

## **Choose a Multidisciplinary Pain Program**

To regain control of your life, it is important to learn how to cope with chronic pain. Although your pain may never go away, it is possible to reduce pain levels and, more importantly, to improve the quality of your life.

To do so, you may need a multidisciplinary approach to chronic pain. While many people with pain have tried every available medical intervention without great success, sometimes these therapies are most effective when performed together in a controlled setting.

A multidisciplinary pain program can provide you with the necessary skills, medical intervention, and direction to effectively cope with chronic pain. Here is advice on how to locate a pain management program in your area, what to look for in a well-defined pain program, and what other issues to consider.

## **Consumer Guidelines to Selecting a Pain Unit**



Make sure you locate a legitimate program

Hospitals and rehabilitation centers are more likely to offer comprehensive treatment than are "stand alone" programs.



Facilities that offer pain management should include several specific components, listed below

The Commission on Accreditation of Rehabilitation Facilities Toll Free Telephone: (800) 281-6531 can provide you with a listing of accredited pain



programs in your area (your health insurance

may require that the unit be CARF accredited in order for you to receive reimbursement).

You can also contact the American Pain Society, an organization for health



care providers, at (847) 375-4715 additional information about pain units in your area.



American Pain Foundation\_Toll-Free at 1-888-615-PAIN (7246)



Choose a good program that is convenient for you and your family:



Most pain management programs are part of a hospital or rehabilitation center. The program should be housed in a separate unit designed for pain management.



Choosing a program close to your home will enable you to commute to the program each day.



Learn something about the people who run the program:

Try to meet several of the staff members to get a sense of the people you will be dealing with while on the unit. The program should have a complete medical staff trained in pain management techniques including:

- ◆ Physician (a neurologist, psychiatrist, physiatrist, or anesthesiologist with expertise in pain management)
- ◆ Registered nurse
- ◆ Psychiatrist or psychologist
- ◆ Physical therapist
- ◆ Occupational therapist
- ◆ Biofeedback therapist
- ◆ Family counselor
- ◆ Vocational counselor
- ◆ Massage Therapy
- ◆ Other personnel trained in pain management intervention

## **Make sure the program includes most of the following features:**

- ◆ Biofeedback training
- ◆ Group therapy
- ◆ Counseling
- ◆ Occupational therapy
- ◆ Family counseling
- ◆ Assertiveness training
- ◆ TENS units
- ◆ Regional anesthesia (nerve blocks)
- ◆ Physical therapy (exercise and body mechanics training, not massage, whirlpool, etc.)
- ◆ Relaxation training and stress management
- ◆ Educational program covering medications and other aspects of pain and its management
- ◆ Aftercare (follow-up support)

## **Be sure your family can be involved in your care:**

- ▶ Family members should be required to be involved in your treatment.
- ▶ The program should provide special educational sessions for family members.
- ▶ Joint counseling for you and your family should also be available.

## **Also consider these additional factors:**

- ▶ What services will your medical insurance reimburse and what will you be expected to cover?
- ▶ Will you need a PCP referral?
- ▶ What is the unit's physical set-up (is it in a patient care area or in an area by itself)?
- ▶ What is the program's length?

- ▶ Is the program inpatient or outpatient
- ▶ If you choose an out-of-town unit, can your family be involved in your care?
- ▶ Do you understand what will be required of you (responsibility to take care of personal needs, etc.)?
- ▶ Does the unit provide any type of job retraining?

Make sure that, before accepting you, the unit reviews your medical records and gives you a complete physical evaluation to be sure you can participate in the program. Obtain copies of your recent medical records to prevent duplicate testing. Try to talk with both present and past program participants to get their feedback about their stay on the unit. Pain programs are difficult, but pain management can make a significant difference in your life. You must realize, however, that much of what you gain from comprehensive pain management will be up to you.

Your pain physician may suggest that you use certain over-the-counter pain relievers or may prescribe stronger medicine for your condition. Do not mix pain prescription drugs with over the counter pain relievers without consulting your physician. Advise your doctor if you are taking any herbal medicines or dietary supplements.

▶ **Common pain relievers** - Nonaspirin pain relievers such as acetaminophen (Tylenol®) can relieve headaches and minor pain but do not reduce swelling. They are sometimes used in combination with other drugs to provide greater pain relief.

▶ **Anti-inflammatory drugs** - Aspirin (Anacin®, Bayer®), coated or buffered aspirin (Ascripton®, Bufferin®) and aspirin with acetaminophen (Excedrin®) may be used to reduce swelling and irritation as well as to relieve pain. There also are non-steroidal anti-inflammatory drugs (NSAIDs, commonly called "N-sayeds") such as ibuprofen (Advil®, Motrin®) and naproxen (Aleve®). Anti-inflammatory drugs are used to relieve pain, inflammation and fever. There also are steroidal drugs (like cortisol and prednisone), available only by prescription, that are used to treat more serious inflammatory conditions such as chronic arthritis.

▶ **Opioid pain medications** - Morphine-like drugs called opioids are prescribed to treat acute pain or cancer pain. They are occasionally used for certain chronic, noncancer pain as well.

▶ **Anti-depressants** - These drugs were originally used only to treat depression. Studies now show, however, that they also can relieve certain pain. Available only by prescription, they often are used to help you sleep better at night.

▣ **Anti-seizure medicines** - These medications are used to relieve what some patients describe as "shooting" pain by decreasing abnormal painful sensations caused by damaged nerves.

▣ **Other medicines** - The doctor may also prescribe other types of medication that will be helpful for your specific pain problems. In addition, medications that counteract the side effects of opioids or treat the anxiety and depression associated with pain may also be prescribed.

Medication alone may not be enough to manage certain kinds of pain. Some medicines are more effective in fighting pain when they are combined with other methods of treatment.

▣ **Injection treatments** - Local anesthetics (such as Novocain®), with or without cortisone-like medicines, can be injected around nerve roots and into muscles or joints. These medicines reduce swelling, irritation, muscle spasms and abnormal nerve activity that can cause pain.

▣ **Nerve blocks** - Often a group of nerves, called a plexus or ganglion, that causes pain to a specific organ or body region can be blocked with local anesthetics. If successful, another solution that numbs the nerves can then be injected.

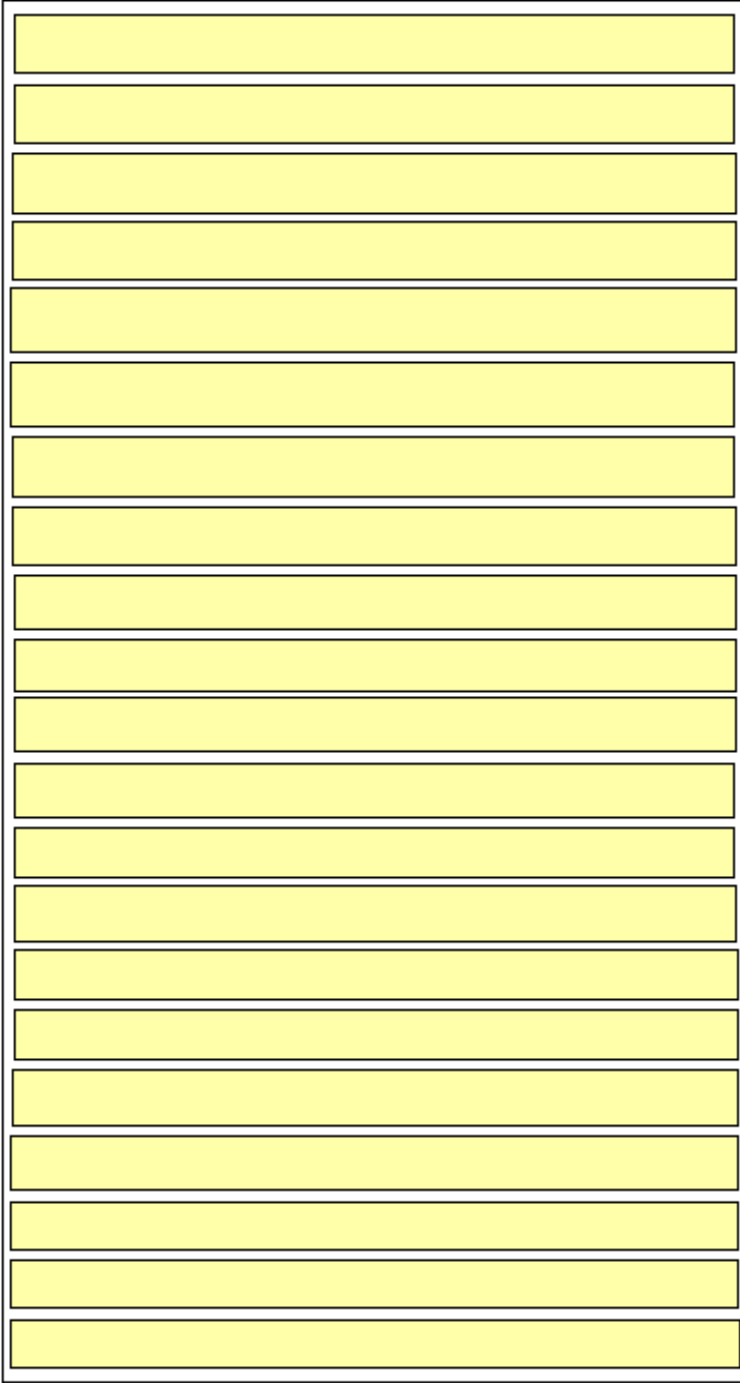
▣ **Physical and aquatic therapy** - The physiatrist or physical therapist may suggest an exercise program tailored for you that will increase your daily functioning and decrease your pain. Other treatments may include whirlpool therapy, ultrasound and deep-muscle massage.

▣ **Electrical stimulation** - Transcutaneous electrical nerve stimulation (TENS) is the most common form of electrical stimulation used in pain management. It is not painful and does not require needles or medicine. TENS consists of a small, battery-operated device that can diminish pain by stimulating nerve fibers through the skin.

▣ **Acupuncture** - This ancient Chinese practice uses very thin needles at very specific points on the skin to treat disease and pain. Practitioners of acupuncture undergo specialized training in these techniques and may offer this treatment for certain painful conditions.

▣ **Psychological support** - Many patients who are in pain feel the emotional effects of suffering along with the physical aspects of pain. These may include feelings of anger, sadness, hopelessness or despair. In addition, pain can alter one's personality, disrupt sleep, interfere with work and relationships and often have a profound effect on family members. Support and counseling from a psychiatrist or psychologist, combined with a comprehensive pain treatment program, may be needed to help you manage your condition. These trained professionals also can teach you additional self-help therapies such as relaxation training or biofeedback to relieve pain, lessen muscle spasms and reduce stress.

▣ **Surgery** - When necessary, surgery may be recommended.

[illegible][illegible]

The MHE Research Foundation would like to acknowledge and thanks the American Pain Foundation for the use of the Keeping A Pain Diary.

## **Keeping A Pain Diary**

You are the only one who knows how much pain you are feeling. When your doctor asks you about the pain, you probably won't remember how hard some days were. You may not remember how bad the pain was. The diary is to help you describe what is happening to you while it is happening. It will be very helpful to your doctor to know when the pain was bad, what made you feel better, and what didn't make you feel better.

Don't worry about how much to write. You don't even have to write sentences. Just write the words that describe how you are feeling. Don't worry if you miss a day. Do it when you can. If thinking about your pain every day is too hard, put the diary away for a few days and go back to it when you are ready. This is your diary. Write when you can for as many days as you can and then stop.

Keep a small notebook or tape recorder with you all day and, during the course of the day, write down what you are feeling. The following questions might help you. Write the date and time every time you write in the diary. If writing is too painful, ask a family member or friend to do it for you or record the diary on a tape recorder.

- 1. Where does it hurt?** List every place that hurts. Does the pain move? Does the pain feel different in different places?
- 2. How does the pain feel?** The following words might be helpful: burning, stabbing, sharp, aching, throbbing, tingling, dull, pounding, or pressing.
- 3. Did you have pain when you woke up or did it start later?**
- 4. Does the pain change during the day?**
- 5. What, if anything, makes the pain better or worse?**
- 6. What medicines are you taking? Do they help—never, sometimes, always?**  
List all of the medicines your doctor gave you and all of the medicines you bought for yourself at the store.
- 7. Have you stopped taking any medicines because they made you constipated, sleepy or sick, or for other reasons?**
- 8. Do you do anything to help make the pain go away other than taking medicine such as getting a massage, or meditating, etc.?**
- 9. Do you have trouble sleeping because of the pain?**
- 10. Does the pain keep you from spending time with family or friends?**
- 11. Do you skip meals because of the pain?**
- 12. How has the pain changed your life?**

## **Additional Publications**

The MHE Research Foundation would like to acknowledge and the University of Pennsylvania Orthopaedic Journal and John Dormans, M.D. for this use of the reprinting of 14: 39–48, 2001 Hereditary Multiple Exostoses: A Current Understanding of Clinical and Genetic Advances authored by J. R. STIEBER, B.A.,<sup>1</sup> K. A. PIERZ, M.D.,<sup>2</sup> AND J. P. DORMANS, M.D.<sup>3</sup>  
<http://www.uphs.upenn.edu/ortho/oj/2001/pdf/oj14sp01p39.pdf>

The MHE Research Foundation would like to acknowledge and thank CLINICAL ORTHOPAEDICS AND RELATED RESEARCH, Lippincott Williams & Wilkins, Inc, and Dr. John Dormans for this use of the reprinting of Number 401, pp. 49–59, 2002 Hereditary Multiple Exostoses: One Center's Experience and Review of Etiology authored by K. A. Pierz, MD\*; J. R. Stieber, MD\*\*K. Kusumi, PhD<sup>†</sup>,<sup>‡</sup>; and J. P. Dormans, MD\*\*,<sup>‡</sup>  
<http://www.clinorthop.org/index.html>

The MHE Research Foundation would like to acknowledge and thank Orphanet Journal of Rare Diseases, Judith VMG Bovée, M.D., Ph.D.; licensee BioMed Central Ltd. for the use of the reprint of Review Multiple Osteochondromas authored by Judith VMG Bovée, Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands  
<http://www.ojrd.com/content/3/1/3>

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

J. R. STIEBER, B.A.,<sup>1</sup> K. A. PIERZ, M.D.,<sup>2</sup> AND J. P. DORMANS, M.D.<sup>3</sup>

## 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<sup>5</sup>. 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 chondrosynplasia, dyschondroplasia, exostosing disease, exos-

totic dysplasia, hereditary deforming chondrodysplasia, multiple osteomatosis, 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

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children or incomplete removal of the cartilaginous cap [35].

### Clinical Manifestations

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].

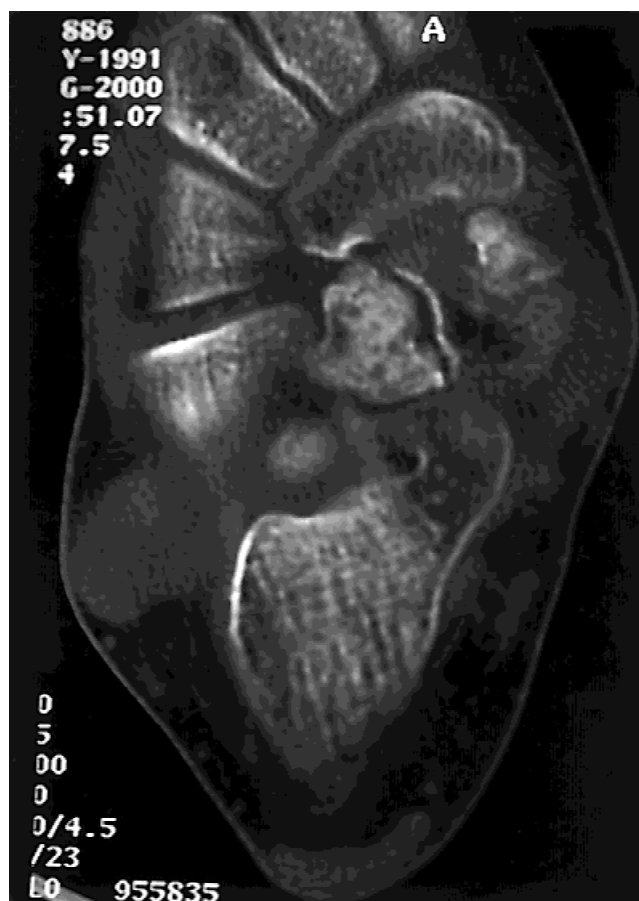
Individuals with HME are frequently of short stature, with most having heights 0.5 to 1.0 SD below the mean [71,75]. Affected adult males and females have been observed to have heights below the fifth percentile in 36.8% and 44.2% of cases, respectively [97]. Sitting height is generally less abnormal 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 anteversion 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-



**Fig. 1.** CT image through the hindfoot showing a tarsal osteochondroma extending from the infralateral border of the talus.

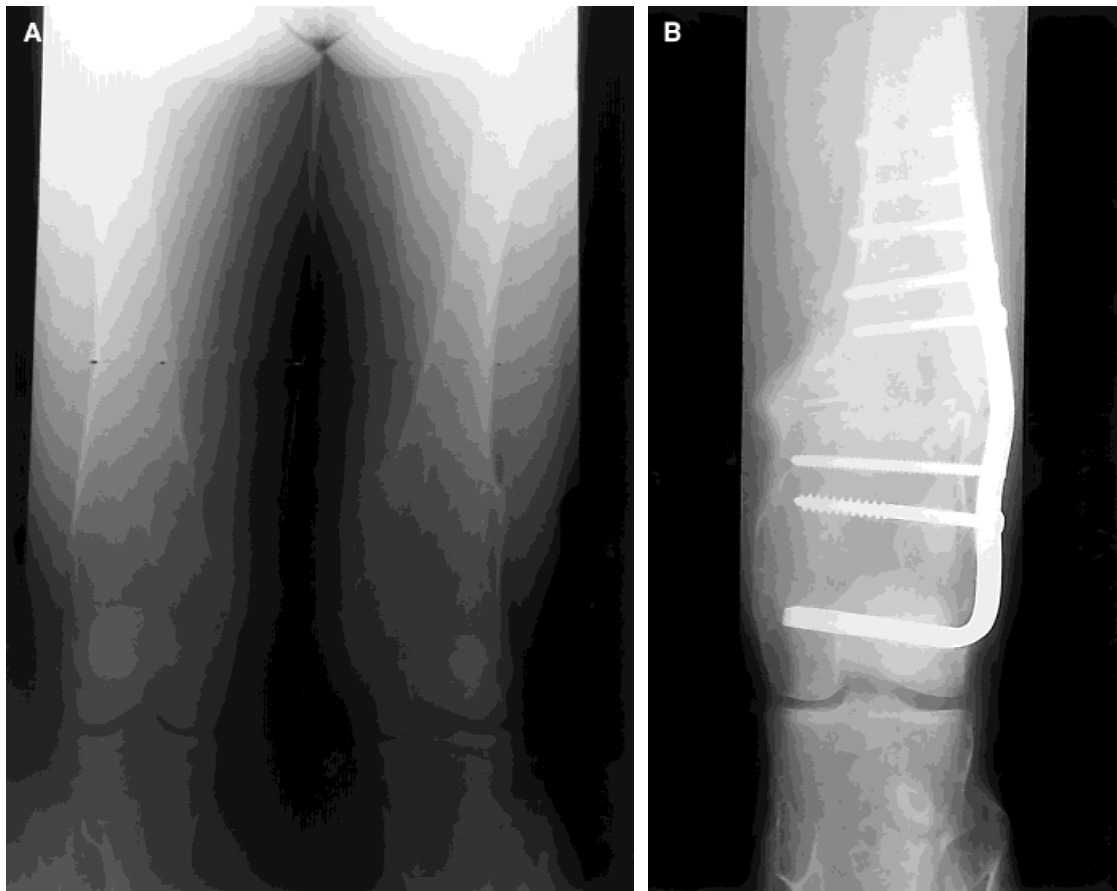
sis [74]. Early medial hemiepiphyseal stapling of the tibia in conjunction with exostosis excision can correct a valgus deformity at the ankle of  $15^\circ$  or greater associated with limited shortening of the fibula [71,74]. Fibular lengthening has been used effectively for severe valgus deformity 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 rela-

tive 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.



**Fig. 3.** A/P radiograph of an ankle demonstrating osteochondromas of the distal tibia and fibula with relative fibular shortening resulting in valgus angular deformity.

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 carpal 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 hemiepiphyseal 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%,



**Fig. 4.** A/P radiograph of the forearm showing ulnar shortening and radial head dislocation.



**Fig. 5.** (A) P/A radiograph of distal forearms showing characteristic radial bow and ulnar shortening of the left wrist. (B) Early postoperative P/A radiographs of the left wrist following corrective osteotomy and pinning. (C) One-year follow-up P/A radiographs of the same wrist showing radial correction with residual ulnar shortening.

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 malignancy. Additionally, the presence in an adult of an osteochondroma with a cartilaginous cap greater than 2 cm has been associated with an increased chance of malignancy [22].

### 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 8q23-q24 [20], EXT2 on 11p11-p12 [102,104], and EXT3 on chromosome 19p [45]. According to linkage analysis, the EXT1 and EXT2 loci appear to be altered in the majority of fami-

lies while, EXT3, which has not been fully isolated and characterized, is probably less frequently affected [105]. Epidemiologic analysis of linkage and mutation data indicate that mutations of EXT1 and EXT2 are likely to be responsible respectively for one half and one third of multiple hereditary exostoses cases [60,61,67,96,106].

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: EXTL1 on chromosome 1p36 [99], EXTL2 on 1p11-p12 [107], and EXTL3 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 EXTL2 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 inactivate 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; EXTL1 has been localized to 1p36, which is often a site of deletion in tumors, and EXTL3 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 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 physis or to a failure of a thin cortical sleeve of bone acting as a structural constraint allowing a spill-over of physeal 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 periosteal differentiation in which ectopic collections of cartilage cells arise from the proliferative layer of the metaphyseal periosteum [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 physeal chondrocytes that persist in chondrogenesis as they are transformed into the proliferative layer of the metaphyseal periosteum [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.

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## Hereditary Multiple Exostoses: One Center's Experience and Review of Etiology

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Hereditary multiple exostosis is a genetic disorder characterized by multiple osteochondromas that can cause pain, deformity, and potential malignant degeneration. Linkage analysis has identified a family of EXT genes which, if mutated, can lose heterozygosity and potentially cause osteochondromas. A database was established of 43 patients with hereditary multiple exostoses treated at a tertiary pediatric healthcare system. Twenty patients had a known family history of the disorder. All patients were diagnosed between birth and 13 years. Symptoms or deformity were observed in the forearms of 29 patients, the knees of 37 patients, and the ankles of 28 patients. Valgus knee deformity related to hereditary multiple exostoses, previously reported to be attributable to proximal tibial changes alone, resulted from proximal tibial or distal femoral valgus deformi-

ties in this series. Twenty-seven patients required between one and five surgeries to address their lesions. No patient had malignant degeneration of an osteochondroma; however, three patients had first-degree relatives with transformation of an osteochondroma to chondrosarcoma. This database now may be a resource for additional analysis. By correlating specific genetic mutations with clinical manifestations, it may be possible to stratify patients into subtypes of hereditary multiple exostoses and identify genetic markers associated with malignant degeneration.

### List of Abbreviations Used

PGs	proteoglycans
TGF- $\beta$	transforming growth factor-beta
FGF	fibroblast growth factor

### Glossary

EXT1 gene = A ubiquitously expressed gene located on chromosome 8q23-q24 that encodes a 746 amino acid protein proposed to have tumor-suppressor function. Mutations in this gene have been associated with hereditary multiple exostoses.

EXT2 gene = A ubiquitously expressed gene located on chromosome 11p11-p13 that en-

(continues)

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codes a 718 amino acid protein proposed to have tumor-suppressor function. Mutations in this gene have been associated with hereditary multiple exostoses.

EXT3 gene = A gene located on chromosome 19p that has been implicated in a minority of cases of hereditary multiple exostoses.

TRPS1 gene = A gene located on chromosome 8 proximal to the EXT1 gene. Abnormalities at this site may result in trichorhinophalangeal syndrome Type I, a condition characterized by craniofacial and cone-shaped epiphyses. Deletions of the TRPS1 and the EXT1 genes may result in Langer-Giedion syndrome, a condition characterized by multiple exostoses, mental retardation, and craniofacial abnormalities similar to those of trichorhinophalangeal syndrome Type I.

Osteochondromas are the most common bone tumors in children, characterized by cartilage-capped, bony excrescences (exostoses) arising from the metaphyseal ends of rapidly growing long bones.<sup>4,36,51</sup> Although most patients only have one osteochondroma, a subset of individuals are afflicted with hereditary multiple exostoses, a genetic disorder producing numerous osteochondromas that can lead to progressive skeletal deformity. Although the true prevalence remains unknown (because patients with asymptomatic lesions may avoid diagnosis), hereditary multiple exostoses has an estimated prevalence of 0.9 to two per 100,000 in Caucasians, the population most thoroughly documented.<sup>21,33,42</sup> Substantially higher prevalences of 100 and 1310 per 100,000 have been reported in the isolated populations of the Chamorros (Guam) and the Ojibway Indians (Pauiingassi, Manitoba, Canada), respectively.<sup>4,25</sup>

Hereditary multiple exostoses is inherited as an autosomal dominant disorder with apparently full penetrance.<sup>21,36,61</sup> Linkage analysis has identified three genes associated with hereditary multiple exostoses: EXT1 on 8q23-q24,<sup>13</sup> EXT2 on 11p11-p12,<sup>58,61</sup> and EXT3 on 19p.<sup>26</sup> Mutations in EXT1 and EXT2 account for approximately 1/2 and 1/3 of cases of heredi-

tary multiple exostoses, respectively.<sup>20,37,39,41,52,56,58,59</sup> Multiple exostoses also are a distinguishing feature of Langer-Giedion syndrome (trichorhinophalangeal syndrome Type II), which results from a deletion of EXT1 and adjacent TRPS1 genes.<sup>22,30</sup> Although early studies have shown an excess of affected males among populations with hereditary multiple exostoses, more recent studies in nuclear families do not show any evidence of gender predominance.<sup>6,23,36,42,61</sup> The initial observations seem to be attributable to more severe clinical manifestation and complications of hereditary multiple exostoses in males.<sup>56</sup>

The genes encoded by EXT1 and EXT2 are endoplasmic reticulum-resident Type II transmembrane glycoproteins.<sup>31,32</sup> Although EXT1 is expressed ubiquitously in many tissues, the effects of EXT1 mutations seem limited to the growing bone.<sup>20</sup> The localized foci of osteochondromas seem to be caused by sporadic loss of heterozygosity, because of inactivation of the normal allele of EXT1 or EXT2 in the osteochondroma cells.<sup>20,52,59,60</sup> Although EXT1 and EXT2 have been proposed to act as tumor suppressor genes, recent evidence suggests that they instead act to regulate bone growth.<sup>29</sup> EXT mutations may lead to secondary changes within chondrocytes, leading to the progression toward malignant degeneration.<sup>12,29</sup> The EXT1 and EXT2 proteins form a heterooligomeric complex involved in the regulation of cell surface heparan sulfate PGs, a key component of cartilage. Heparan sulfate PGs have been shown to play an integral role in the diffusion of several families of cell-signaling molecules, including those in the Wnt, hedgehog, TGF- $\beta$ , and FGF families.<sup>28</sup> Interestingly, tout-velu, the *Drosophila* homologue of EXT, has been shown to affect the normal diffusion of hedgehog.<sup>3</sup> Among mammalian homologues of hedgehog, Indian hedgehog is expressed by chondrocytes and diffuses into the perichondrium to inhibit differentiation of chondrocytes.<sup>54</sup> Wuyts et al<sup>60</sup> suggested that EXT mutations in hereditary multiple exostoses may act by disrupting the negative-feedback loop of chondrocyte differentiation,

resulting in abnormal and ectopic skeletal development.

The most common clinical problems associated with hereditary multiple exostoses include pain and cosmetic complaints. Additionally, lesions may cause disrupted osseous growth, bowing of the long bones, angulation of the joints, and decreased range of joint motion.<sup>43</sup> The most common deformities described in children with hereditary multiple exostoses 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 subluxation of the carpus, subluxation of the radial head, and relative shortening of the metatarsals, metacarpals, and phalanges.<sup>10,24,42,43,48,56</sup> Scoliosis, coxa valga, and acetabular dysplasia have been described less commonly.<sup>16,43</sup> Skeletal defects may lead to associated soft tissue problems, including tendon, nerve, or vascular irritation or injury.<sup>7,53</sup> Spinal cord compression also is a rare, but well-documented, complication of hereditary multiple exostoses,<sup>2,15,40,44,45</sup> and spontaneous hemothorax as a result of rib exostoses has been described.<sup>9,14</sup> Although osteochondromas usually are benign, clinically and histologically, malignant transformation to chondrosarcoma or other sarcomas is a major complication with a reported incidence ranging from 0.5% to 25%,<sup>18,47,49,53,55</sup> but other reported estimates are 5% or less.<sup>4-6,19,27,42,53,55</sup>

The identification of the genetic basis of hereditary multiple exostoses presents a unique opportunity to extend clinical studies and, potentially, develop therapeutic modalities. The current authors describe the population of patients with hereditary multiple exostoses from a large, tertiary pediatric healthcare system. In establishing a database of patients with hereditary multiple exostoses, a comparison of clinical observations was made with previous studies. The current study highlights the most common locations of lesions and their associated deformities and provides treatment options for symptomatic lesions. Identification of predisposing factors to malignant degener-

ation may be possible through genetic analyses of such patients.

## MATERIALS AND METHODS

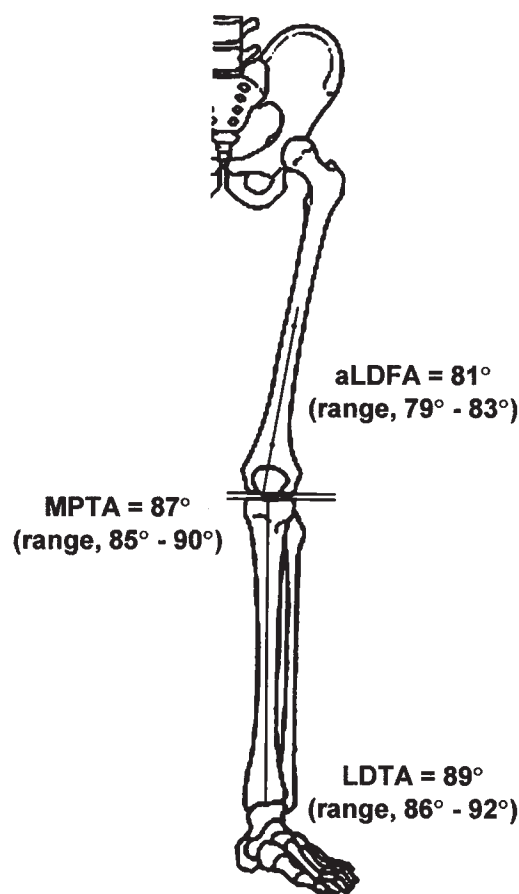
A database was established of all patients diagnosed with hereditary multiple exostoses and treated at the authors' institution from 1991 to 2001. Patients were identified through the established musculoskeletal tumor database with additional information obtained from medical records and the pathology and radiology databases. Of 46 children diagnosed with hereditary multiple exostoses, complete records were available for 43 patients who serve as the basis for this study. Information collected included but was not limited to: the age at diagnosis, family history of the disorder, patient subjective complaints associated with the disorder, the anatomic distribution of exostoses, clinical assessments of deformity, dates and descriptions of orthopaedic surgical procedures, and history of sarcomatous degeneration.

For patients who had surgical excision of prominent or painful exostoses, the degree of deformity was quantified using radiographs obtained preoperatively. Radiographs also were reviewed for patients with limb length inequalities or angular deformities. Anteroposterior (AP) radiographs were used to measure the anatomic laterodistal femoral angle, the medioproximal tibial angle, and the laterodistal tibial angle for patients identified as having deformity<sup>11,35</sup> (Fig 1). By comparing the patients' measurements with normal population measurements, the amount of varus or valgus malalignment was calculated.

## RESULTS

Of the 43 patients diagnosed with hereditary multiple exostoses, 23 (53.4%) were male and 20 (46.5%) were female. Twenty patients (46.5%) had a known family history of hereditary multiple exostoses. Ages at initial diagnosis ranged from birth to 13 years, 3 months (mean, 5 years, 9 months).

The distribution of symptomatic lesions was analyzed for all patients. The number of different anatomic locations was determined rather than the discrete number of lesions present because many patients were affected with



**Fig 1.** Normal lower extremity frontal plane alignment is shown. The anatomic laterodistal femoral angle (aLDFA) is the angle subtended by the intersection of the bicondylar line with a line formed by connecting two central points along the femoral anatomic axis. The medioproximal tibial angle (MPTA) and laterodistal tibial angle (LDTA) are angles formed by the intersection of the tibial mechanical axis with the proximal and distal plafonds, respectively.<sup>11,35</sup>

multiple clustered lesions at a given site, which lacked distinct morphologic features. The number of locations affected ranged from two to 27 (mean, 12 locations) per patient.

In the upper extremity, 26 patients (64%) had symptomatic lesions identified in the proximal humerus by the time of the last followup, whereas the distal humerus was in-

involved far less frequently, affecting only three patients (5%). The scapula was symptomatic in 13 patients (30%), and the clavicle was symptomatic in only one patient (2%). The forearm was symptomatic in 29 patients (67%). The radius was symptomatic distally in 27 patients (63%) and proximally in seven patients (16%). The ulna was symptomatic distally in 23 patients (54%) and proximally in six patients (14%).

Twelve patients (28%) complained of a bowed deformity of their forearm (Fig 2). No patient in the current series had a complete radial head dislocation. One patient sustained a pathologic fracture of the distal radius through the stalk of a pedunculated exostosis. The metacarpals were symptomatically affected in 11 patients (26%), and the digits were symptomatic in 19 patients (44%). Five patients complained of decreased range of motion (ROM) of either the proximal interphalangeal or distal interphalangeal joints associated with symptomatic osteochondromas. Six patients had angular deformities of the phalanx with five involving the proximal interphalangeal joint and one involving the distal interphalangeal joint. Additionally, one patient had decreased excursion of the extensor tendon secondary to the presence of an exostosis on the proximal phalanx. No lesions were identified on the carpal bones.

In the lower extremity, 16 patients (37%) had symptomatic lesions of the proximal femur, and 37 patients (86%) had involvement of the distal femur at the last followup. The proximal tibia and fibula were symptomatic in 34 (79%) and 32 (74%) patients, respectively. Seven patients (16%) complained of locking or pseudolocking of their knees, and 12 patients (28%) had peroneal nerve palsies or paresthesias.

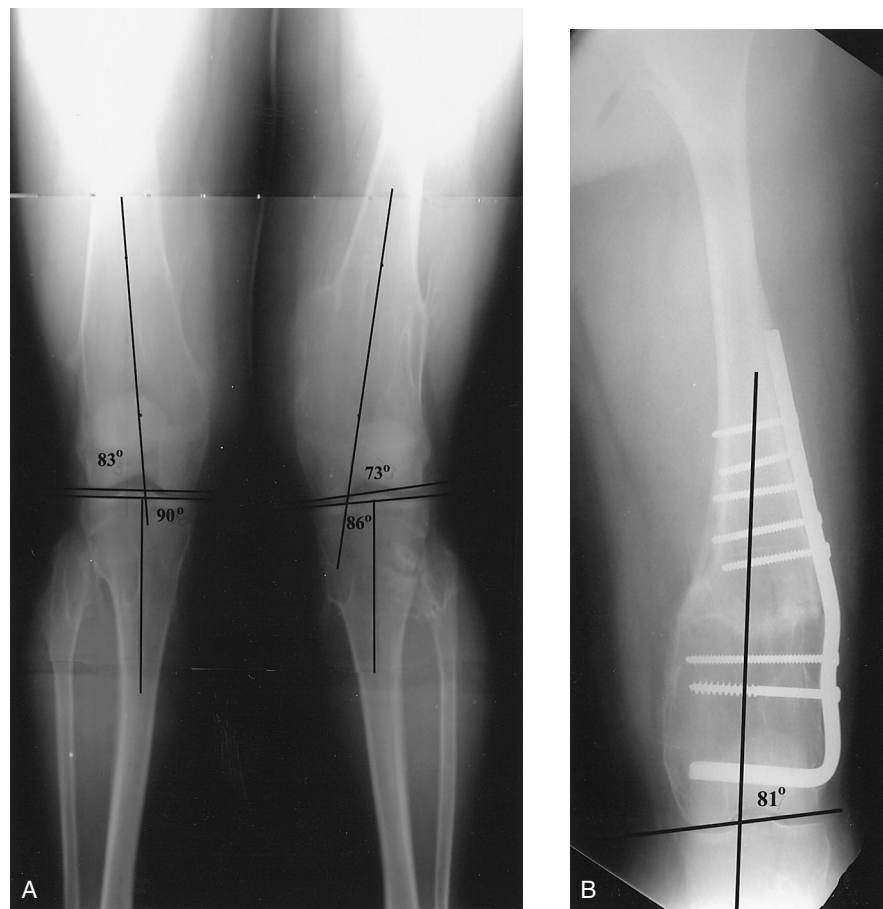
Twenty-two patients (31 knees) had significant knee deformities (Fig 3). Eleven patients (13 knees) had varus angular deformities of the distal femur, and one patient had a varus deformity of the proximal tibia. Seven patients (eight knees) had valgus distal femoral deformities, and 10 patients (16 knees) had valgus proximal tibial deformities. Seven pa-



**Fig 2 A–D.** (A) Anteroposterior and (B) lateral radiographs of the right forearm of a 15-year-old boy with hereditary multiple exostoses show multiple exostoses, ulnar shortening, and ulnar carpal drift. (C) Anteroposterior and (D) lateral radiographs of the left forearm of the same boy show similar deformities.

tients (seven knees) had overall varus knee malalignment, and 14 patients (17 knees) had valgus knee malalignment. Five patients (six femurs) had varus femoral deformities, although their tibias were in valgus. One patient

with a valgus femoral deformity had a coexisting varus proximal tibial deformity. Seven of 31 knees (23%) had near normal overall knee alignment, despite angular deformity of individual bones.



**Fig 3 A–B.** (A) An anteroposterior radiograph of the lower extremity of a 16-year-old girl taken with the patient standing shows multiple exostoses and a left femoral valgus deformity. (B) The valgus was corrected by an opening wedge femoral osteotomy.

Twenty-three patients (54%) complained of some involvement of the ankle with 18 (42%) patients presenting with lesions on the distal tibia and 17 (40%) patients presenting with lesions on the distal fibula. Six patients (14%) had symptomatic exostoses on their metatarsals, and four patients (9%) had symptomatic exostoses on their phalanges. No lesions were seen on the tarsal bones.

Sixteen patients (37%) had symptomatic exostoses identified on their ribs. Three patients (7%) had symptomatic lesions on the spine, and eight patients (19%) had lesions affecting the pelvis.

Twenty-seven patients (63%) had surgical procedures for complaints or deformity associated with hereditary multiple exostoses. Patients in the study had between one and five surgeries (mean, 1.4 surgeries), with the first surgery occurring from 2 years, 4 months to 17 years, 6 months of age (mean, 10 years). Twenty-six patients had an exostosis excised from between one and eight locations (mean, 3.4 locations) by the time of latest followup.

Fourteen patients (15 forearms) had surgery on their forearms, and all had excision of at least one exostosis on the distal radius or ulna. Three patients had osteotomies of the distal ra-

dius for treatment of radial bowing. Five patients had ulnar lengthening procedures, whereas one patient required a distal ulnar resection. Four patients had surgical procedures on a phalanx: four had exostoses excised, and one patient had the proximal phalanx treated with pin fixation.

Three patients (four hips) experienced decreased ROM of the hip, but only two of these patients required excision of the exostosis from their proximal femur. Although a leg length discrepancy of at least 2 cm was seen in nine patients (21%), no patient had surgery solely for this discrepancy. For patients with coexisting angular deformities requiring surgery, an attempt was made to address the discrepancy simultaneously.

Twenty patients (27 knees) had deformities about the knee for which they required surgery. Nineteen of these patients had at least one excision of an exostosis from the distal femur, the proximal tibia, or the proximal fibula. Exostoses were excised from six patients (seven femurs) with varus distal femurs and two patients with valgus distal femurs, including one patient who was treated additionally with a distal femoral opening wedge osteotomy and blade-plate fixation to correct the valgus deformity (Fig 3). Exostoses were excised from the prox-

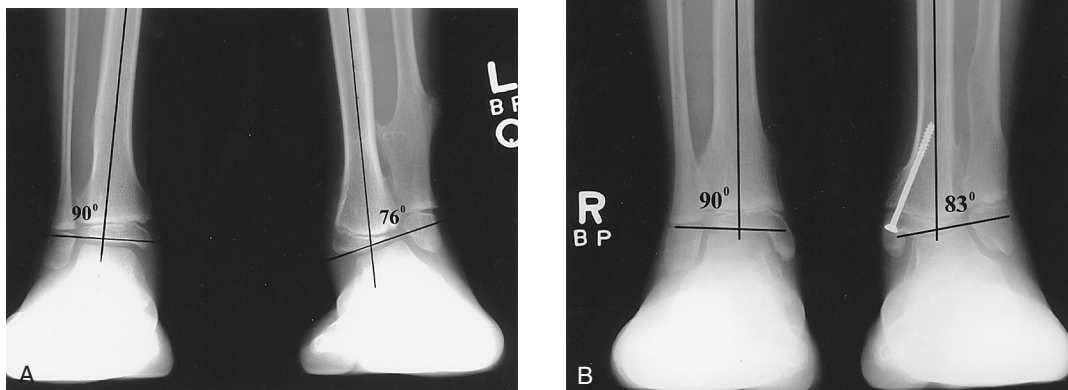
imal fibula in 12 patients (15 knees). Six patients (seven tibias) had excision of symptomatic exostoses from their valgus proximal tibias. Two of these patients had additional surgical correction of the angular deformity: one patient was treated with a hemiepiphysiodesis of the proximal tibia and the other patient was treated with a high tibial osteotomy.

Fifteen patients (22 ankles, or 54%) had valgus deformities, whereas none of the patients had varus deformities. Two patients (three ankles) had operative treatment of valgus ankle deformities. One patient received corrective osteotomies, and the other patient had a medial malleolar screw placed to arrest medial overgrowth (Fig 4). Two patients had widening of their syndesmoses, and one experienced a synostosis.

There were no cases of chondrosarcoma or osteosarcoma in any of the children being followed up in this series. At least three patients, however, had first-degree relatives with malignant degeneration of an osteochondroma to a chondrosarcoma.

## DISCUSSION

Hereditary multiple exostoses is a disorder known to cause deformity, pain, and potential



**Fig 4 A–B.** (A) An anteroposterior radiographs of the ankles of a 7-year-old girl taken with the patient standing show left ankle valgus. (B) Treatment with a medial transphyseal screw allowed for continued lateral growth to correct the deformity as seen in this radiograph taken 2 years, 10 months after surgery.

malignant degeneration. Although loss of heterozygosity in the EXT1 or EXT2 genes has been implicated in causing osteochondroma formation, the mechanism by which certain osteochondromas undergo malignant transformation to chondrosarcomas remains to be elucidated fully.

In the current series, no patient had malignant degeneration of an osteochondroma; however, family histories of three patients revealed first-degree relatives with osteochondromas that had malignant degeneration to chondrosarcomas during adulthood. Ochsner<sup>34</sup> published a report of 59 patients with hereditary multiple exostoses who had malignant transformation. The mean age at diagnosis of malignancy was 31 years, with malignant degeneration seldom occurring in the first decade or after the fifth decade of life. Consistent with this, it would be unlikely to find cases of chondrosarcoma in this pediatric population. The reported incidence of malignant degeneration varies considerably, ranging from 0.5% to 25%.<sup>18,47,53,55</sup> This variation can be attributed not only to the possible selection bias inherent for a tertiary referral center, but also to the difficulty in diagnosing patients with asymptomatic hereditary multiple exostoses, making it difficult to determine the true denominator of patients.<sup>8</sup> Several studies estimate the rate of secondary malignancy to be 5% or less.<sup>4,19,27,42,53</sup> The risk of malignant transformation may vary among families because of the genetic heterogeneity of the disorder.<sup>42</sup> Carroll et al<sup>8</sup> tried to correlate phenotypic patterns with three different genotypes in an attempt to help predict which patients may be at greatest risk and potentially explain the wide variance of malignant transformation reported.

In the current study, 15 patients (35%) presented with symptoms or deformity of the upper extremity. The prevalence of such deformities has been reported to be as high as 40% to 60%.<sup>23,42,43,48,57</sup> Taniguchi<sup>50</sup> tried to correlate forearm involvement with overall severity of hereditary multiple exostoses. Porter et al<sup>38</sup> theorized that early ablation of juxtaphyseal lesions may minimize future growth retarda-

tion. In one study of 25 patients who were treated surgically to correct forearm deformities, Fogel et al<sup>17</sup> reported that ulnar lengthening could improve ulnar translocation of the carpus on the distal radius, but relative ulnar shortening often recurs. They also concluded that, in cases of more substantial bowing, distal radial osteotomy or hemiepiphyseal stapling in addition to exostosis excision is necessary to improve function and cosmesis. In the current study, three patients were treated satisfactorily for radial bowing with a distal radius osteotomy and five patients were treated satisfactorily with ulnar lengthening procedures. Similar to the findings of Fogel et al,<sup>17</sup> the current study showed that although early osteochondroma excision alone may decrease or halt progression of forearm deformity, it does not consistently provide full correction. The functional consequences of surgical intervention remain unclear. Arms et al,<sup>1</sup> using a questionnaire, concluded that skeletally mature patients with hereditary multiple exostoses function well despite their forearm deformity; however, these authors continue to offer surgery to improve aesthetic appearance and provide pain relief.

The high rate of knee deformity (37 knees, or 86%), although slightly less than the 94% reported by Schmale et al,<sup>42</sup> is consistent with the high rates reported in other published studies.<sup>43,48</sup> The rate of valgus knee deformity in this population (13 of 47, or 28%) also is consistent with previous series.<sup>33,42,43</sup> Unlike previous reports that have suggested that the valgus knee deformity seen in patients with hereditary multiple exostoses only is attributable to proximal tibial changes,<sup>33,43</sup> the current study revealed that the distal femur and proximal tibia contribute to the deformity. One patient with a substantially valgus distal femur (anatomic laterodistal femoral angle of 73°) was treated satisfactorily with an opening wedge osteotomy and bladeplate fixation (Fig 3). Two patients with valgus proximal tibias were treated satisfactorily with a hemiepiphysiodesis or a high tibial osteotomy. None of the patients in this series experienced frank

patellar dislocation, which has been documented as a potential complication of valgus knee deformity in patients with hereditary multiple exostoses.<sup>33</sup> A substantial number of patients with knee deformities (seven of 31, or 23%) had opposing angular deformities of their distal femurs and proximal tibias, which compensated to produce near normal overall knee alignment. Such patients may have progressive changes in the distal femur and proximal tibia that are not clinically apparent on physical examination, because the changes in the anatomic lateral distal femoral angle and the medial proximal tibial angle complement each other to maintain a normal mechanical axis. The knee geometry in these patients may affect the load distribution on the weightbearing surfaces of the joint and, potentially, lead to degenerative joint disease.

In the current study, the incidence of valgus ankle deformity (22 of 41, or 54%) was similar to that observed in several series.<sup>24,43,47</sup> Snearly and Peterson<sup>46</sup> reported that in more advanced cases, excision of exostoses alone does not correct the ankle deformity, although it may improve preoperative symptoms and cosmesis. In the current series, one patient with severe, bilateral valgus ankle deformities was treated successfully with supra-malleolar osteotomies, and this treatment was shown to be an effective treatment of this deformity in patients with hereditary multiple exostoses.<sup>43</sup>

The current study was done to identify the population of patients with hereditary multiple exostoses treated at a tertiary pediatric hospital and to compare this group with those reported in previous studies. By establishing a database of patients in this study, the initial steps have been taken toward establishing a resource for additional genetic analysis. By correlating specific genetic markers with clinical manifestations, it may be possible to stratify patients into hereditary multiple exostoses subtypes and identify additional genetic modifiers leading to susceptibility for malignant degeneration. Such information could be used to identify key patients at risk who would re-

quire more vigilant followup into adulthood, and investigate the genetic mechanisms leading to malignant transformation.

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Review

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## Multiple osteochondromas

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### Abstract

Multiple osteochondromas (MO) is characterised by development of two or more cartilage capped bony outgrowths (osteochondromas) of the long bones. The prevalence is estimated at 1:50,000, and it seems to be higher in males (male-to-female ratio 1.5:1). Osteochondromas develop and increase in size in the first decade of life, ceasing to grow when the growth plates close at puberty. They are pedunculated or sessile (broad base) and can vary widely in size. The number of osteochondromas may vary significantly within and between families, the mean number of locations is 15–18. The majority are asymptomatic and located in bones that develop from cartilage, especially the long bones of the extremities, predominantly around the knee. The facial bones are not affected. Osteochondromas may cause pain, functional problems and deformities, especially of the forearm, that may be reason for surgical removal. The most important complication is malignant transformation of osteochondroma towards secondary peripheral chondrosarcoma, which is estimated to occur in 0.5–5%. MO is an autosomal dominant disorder and is genetically heterogeneous. In almost 90% of MO patients germline mutations in the tumour suppressor genes *EXT1* or *EXT2* are found. The *EXT* genes encode glycosyltransferases, catalyzing heparan sulphate polymerization. The diagnosis is based on radiological and clinical documentation, supplemented with, if available, histological evaluation of osteochondromas. If the exact mutation is known antenatal diagnosis is technically possible. MO should be distinguished from metachondromatosis, dysplasia epiphysealis hemimelica and Ollier disease. Osteochondromas are benign lesions and do not affect life expectancy. Management includes removal of osteochondromas when they give complaints. Removed osteochondromas should be examined for malignant transformation towards secondary peripheral chondrosarcoma. Patients should be well instructed and regular follow-up for early detection of malignancy seems justified. For secondary peripheral chondrosarcoma, *en-bloc* resection of the lesion and its pseudocapsule with tumour-free margins, preferably in a bone tumour referral centre, should be performed.

### Disease name and synonyms

Multiple Osteochondromas (MO) MIM 133700

Hereditary Multiple Exostoses (HME), Multiple Hereditary Exostoses (MHE), EXT, diaphyseal aclasis, (multiple hereditary) osteochondromatosis, multiple cartilaginous exostoses

### Definition and diagnostic criteria

Osteochondroma (osteocartilaginous exostosis) is a cartilage capped bony projection arising on the external surface of bone containing a marrow cavity that is continuous with that of the underlying bone [1]. A diagnosis of MO can be made when radiologically at least two osteochondromas of the juxta-epiphyseal region of long

bones are observed. In the majority of patients a positive family history and/or mutation in one of the *EXT* genes can be detected [2,3].

### Epidemiology

The prevalence of MO is estimated at 1:50,000 persons within the general population [4] and seems to be higher in males (male-to-female ratio 1.5:1) [2,5]. This is probably due to the fact that females tend to have a milder phenotype and are therefore more easily overlooked [2]. The solitary (sporadic) form of osteochondroma is approximately six times more common than the occurrence within the context of MO. Approximately 62% of the patients with multiple osteochondromas have a positive family history [2].

### Clinical description

Osteochondromas develop and increase in size in the first decade of life, ceasing to grow when the growth plates close at puberty. They are pedunculated or sessile (broad base) and can vary widely in size. The majority are asymptomatic and located in bones that develop from cartilage, especially the long bones of the extremities, predominantly around the knee (Figures 1 and 2A). The facial bones are not affected. The number of osteochondromas may vary significantly within and between families, the mean number of locations is 15–18 [6]. In addition, in MO patients a variety of orthopaedic deformities can be found like deformities of the forearm (shortening of the ulna with secondary bowing of radius) (39–60%) [4,6,7] (Figure 2C), inequality in limb length (10–50%) [4,7], varus or valgus angulation of the knee (8–33%) [4,7],



**Figure 1**  
Photograph of the legs of a 26 year old male showing multiple lumps leading to deformity.

deformity of the ankle (2–54%) [4,7] and disproportionate short stature (37–44%) [2,5,6].

Other complications of the osteochondromas include osseous and cosmetic deformities, bursa formation, arthritis (14%) [5] and impingement on adjacent tendons, nerves (22.6%) [5], vessels (11.3%) [5] or spinal cord (0.6%) [5,8]. MO patients may have abnormal scar formation [9]. Osteochondromas bear the risk for fracture of the bony stalk during physical exercise. This is estimated to occur in approximately 5% of osteochondromas [10] and may be reason for surgical removal.



**Figure 2**  
Examples of radiographs demonstrating multiple osteochondromas around the knee (A) and at the pelvis and proximal femur (B), while (C) demonstrates the deformity of the forearm (shortening of the ulna with secondary bowing of radius) that is found in 39–60% of the patients.

The majority of MO patients experiences pain [11,12], approximately half of which concerns generalised pain [11]. Therefore, the number of MO individuals having pain has been underestimated and pain seems a problem that must be addressed when caring for MO patients. The occurrence of pain was associated with MO related complications and surgery [11].

The most important complication of MO is malignant transformation of an osteochondroma, which is estimated to occur in 0.5–5% of patients [2,4,5,13,14]. Clinical signs of malignant transformation include an increase in size and pain [6]. Malignant transformation of osteochondroma leads to a secondary peripheral chondrosarcoma in 94% of the cases [15]. The suspicion of secondary chondrosarcoma is indicated by growth of the tumour after puberty, the presence of pain, or a thickness over 1 cm of the cartilaginous cap in adults.

### Aetiology

Two genes, *EXT1* and *EXT2* located respectively at 8q24 and 11p11-p12, have been isolated to cause MO [16-19]. Additional linkage to chromosome 19p has been found, suggesting the existence of an *EXT3*-gene [20]. However, the gene has never been identified. Moreover, the increased sensitivity of mutation detection and the use of new techniques screening for larger deletions, such as MLPA, have dramatically decreased the proportion of MO patients without an *EXT1* or *EXT2* mutation to <15% [21-23]. These data question the existence of an *EXT3*-gene at 19p.

The *EXT1* gene is composed of 11 exons and has a coding region of 2238 bp [17-24]. The *EXT2*-gene contains 16 exons [18,19] and its cDNA defines a single open reading frame of 2154 bp. *EXT1* and *EXT2* are highly similar, especially in the carboxy terminal region [18,19].

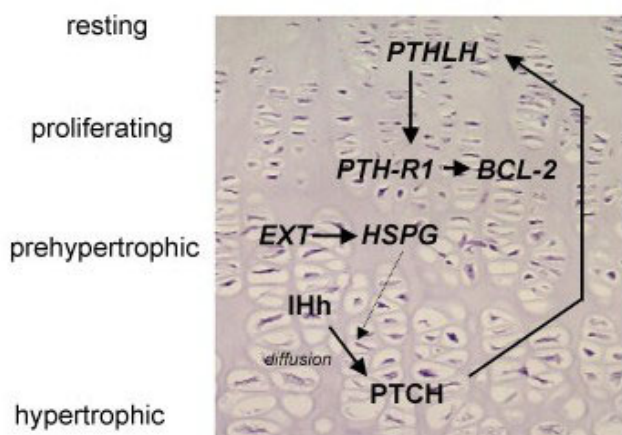
The *EXT1* gene was reported to show linkage in 44%–66% of the MO families [25,26], whereas *EXT2* would be involved in 27% [26]. Germline mutations of *EXT1* and *EXT2* in MO patients have been studied extensively in Caucasian as well as Asian populations [27]. In *EXT1*, mutations are more or less randomly distributed over the first 6 exons, while the last 5 exons, containing the conserved carboxyterminal region, contain significantly less mutations [27]. Similarly, in *EXT2* most mutations are found in the first eight exons. No mutational hotspots are found. Approximately 80% of the mutations are either non-sense, frameshift, or splice-site mutations leading to premature termination of EXT proteins [25,28-32]. The majority of missense mutations also lead to defective EXT protein function [33]. Mutations in *EXT1* seem associated with a more severe phenotype as compared to *EXT2* [34-37].

It has long been thought that osteochondromas are the result of skeletal dysplasia. It is now however generally accepted that osteochondromas are neoplastic, since genetic changes are found in the cartilage cap [1,38-42]. The *EXT*-genes are tumour suppressor genes. Loss of the remaining *EXT1* wildtype allele has been demonstrated in the cartilage cap of osteochondromas from MO patients [39]. However, in a considerable proportion of MO patients loss of the remaining wildtype allele could not be detected so far [43]. In seven out of eight solitary osteochondromas, homozygous deletions of *EXT1* are found [38] further supporting the two-hit model. Moreover, the deletions were confined to the cartilage cap. Thus, the cartilage cap is the clonal neoplastic element, while the stalk is reactive [38].

Both *EXT1* and *EXT2* mRNA is ubiquitously expressed [17-19]. A high level of expression of *Ext1* and *Ext2* mRNA has been found in developing limb buds of mouse embryos [44,45] and expression was demonstrated to be confined to the proliferating and prehypertrophic chondrocytes of the growth plate [46]. In osteochondromas and peripheral chondrosarcomas the expression of *EXT1* and/or *EXT2* is decreased, corresponding to the mutation status [47].

The gene products, exostosin-1 (*EXT1*) and exostosin-2 (*EXT2*), are endoplasmic reticulum localized type II transmembrane glycoproteins which form a Golgi-localised hetero-oligomeric complex that catalyzes heparan sulphate (HS) polymerization [48-51]. Heparan sulphate proteoglycans (HSPG) are large macromolecules composed of heparan sulphate glycosaminoglycan chains linked to a protein core. Four important HSPG families are syndecan, glypican, perlecan and isoforms of CD44 bearing variable exon 3 (CD44v3). In osteochondromas in which EXT expression is decreased due to mutation or deletion, the heparan sulphate proteoglycans seem to accumulate in the cytoplasm of the cell, instead of being transported to be expressed at the cell surface [47].

EXT and HSPGs are required for high-affinity binding of fibroblast growth factor to its receptor and for the diffusion of the morphogens Hedgehog (Hh, human homologues Indian (IHH) and Sonic Hedgehog (SHH) [52-54], decapentaplegic (dpp, human homologues TGF-beta and BMP) and wingless (wng, human homologue Wnt) [55,56]. These three pathways are important during development and are specifically active in the growth plate during endochondral bone formation. During normal growth, IHH and PTHLH are involved in a delicate paracrine feedback loop regulating proliferation and differentiation of the chondrocytes of the growth plate (Figure 3). In osteochondroma, IHH signalling is still active and is probably cell autonomous [57,58]. PTHLH signalling,

**Figure 3****Growth plate signaling in the normal growth plate.**

Indian Hedgehog protein (IHh) is expressed in the prehypertrophic cells, and diffuses over a variable distance to its receptor Patched (PTCH). Subsequently, increased secretion of ParaThyroid Hormone Like Hormone (PTHLH) is induced at the apical perichondrium via an incompletely understood mechanism. PTHLH then diffuses to its receptor, whose expression is restricted to the late proliferating chondrocytes, inhibiting their further differentiation, resulting in less IHh producing cells, which closes the feedback loop. Thus, PTHLH regulates the pace of chondrocyte differentiation by delaying the progression of chondrocytes towards the hypertrophic zone, allowing longitudinal bone growth. Defective or absent EXT proteins leading to altered or absent HSPG expression at the cell surface may affect this negative feedback loop by disturbing the diffusion of IHh, produced at the pre-hypertrophic chondrocytes, towards its receptor Ptc.

which is downstream of IHH and is responsible for chondrocyte proliferation, is absent in osteochondroma, while being upregulated upon malignant transformation of osteochondroma [59,60]. Wnt signalling and TGF-beta signalling are also active in the majority of osteochondromas [57]. The exact role of EXT in orchestrating these pathways leading to osteochondroma formation in MO patients needs to be further elucidated.

**Diagnostic methods**

When a patient is suspected to have MO, the full radiological documentation, histology (if available), patient history and family history have to be carefully reviewed. Given the specific radiological and histological expertise needed, and the rarity of the disorder and of those in the differential diagnosis, it is recommended that this review is performed by specialists in the field, for instance through a national bone tumour registry consisting of clinicians, radiologists and pathologists. If this review is indicative for MO, the peripheral blood of the patient may be screened for germline mutations in *EXT1* or *EXT2* [61].

In case of a positive family history in which MO is clearly established in relatives, the diagnosis of MO can be clinically made and mutation analysis is not essential. With the currently used methods it is possible to detect point mutations or gross deletions in almost 90% of MO patients [21-23,61-63].

To evaluate possible malignant transformation in case of complaints or growth of the lesion after puberty, the size of the cartilaginous cap can be well established with T2-weighted magnetic resonance (MR) imaging [64]. A cartilage cap >1.5 cm should be regarded with caution. The role of 18 Fluoro-deoxyglucose positron emission tomography (18FDG PET) needs to be further established [65].

**Differential diagnosis**

Dysplasia Epiphysealis Hemimelica (DEH, Trevor's disease, tarso-epiphyseal aklasis) and metachondromatosis (MC) are considered in the differential diagnosis of solitary and hereditary osteochondromas. Despite their similarities, they were shown to be separate entities [66] and the EXT downstream pathway is not involved [67].

DEH is a developmental disorder with cartilaginous overgrowth of a portion of one or more epiphyses [68]. It predominantly affects the lower extremity on one side of the body. It is usually restricted to either the medial (most frequent) or lateral side of the limb (hemimelic). Similar to osteochondroma, DEH is usually diagnosed prior to the age of 15 years, more often in boys than in girls, and growth of these lesions end at puberty as the growth plates close [68,69]. In contrast to MO, malignant transformation has not been reported so far [68] and there does not appear to be any genetic transmission [69-71].

MC is a rare disorder exhibiting, synchronous, both multiple osteochondromas and enchondromas in children. It has an autosomal dominant mode of inheritance [72-74] but the disorder has not been mapped in the human genome so far. MC related osteochondromas characteristically occur in the hands and feet, predominantly the digits and toes, and point toward the adjacent growth plate, while in MO the osteochondromas are mainly located in the long or other tubular bones and point away from the epiphysis [72]. Differentiation from MO is of great clinical significance because in patients with MC the lesions do not result in shortening or deformity of affected bones as in MO, and may spontaneously decrease in size or resolve completely, both clinically and radiologically [72,74].

Moreover, MO should be distinguished from enchondromatosis (Ollier disease and Maffucci syndrome), in which multiple cartilage tumours are found in the medulla of bone, with a predilection for the short tubular bones and a unilateral predominance [75].

Upon histopathological examination of osteochondroma after surgical removal malignancy should be considered. Malignant transformation in the cartilage cap of osteochondroma leads to a secondary peripheral chondrosarcoma. Occasionally, osteosarcomas and spindle cell sarcomas develop in the stalk of the osteochondroma [15,76-80]. Extremely rare is the occurrence of dedifferentiated peripheral chondrosarcoma, in which a low-grade chondrosarcoma that developed within an osteochondroma "dedifferentiates" into a high grade sarcoma [81,82].

### Genetic counselling

MO is an autosomal dominant disorder. Affected individuals have 50% risk of transmitting the disorder to their offspring. MO has nearly 100% penetrance. If the exact mutation is known antenatal diagnosis is technically possible.

### Management including treatment

Osteochondromas are only removed when they cause pain, when they give functional complaints for instance due to compression on nerves or vessels, or for cosmetic reasons.

Surgical treatment of forearm deformities remains controversial. In a retrospective series 23 MO patients corrective osteotomy and/or lengthening of forearm bones was not beneficial [83]. Moreover, one should consider the possible recurrence of ulnar shortening within 1.5 years when operating skeletally immature patients [83,84]. The most beneficial procedure was excision of the osteochondromas. The simple removal of an osteochondroma can improve forearm rotation and correct deformity [83], especially if there is an isolated tumour of the distal part of the ulna.

If the diagnosis of MO is established and all tumours are identified, patients should be well instructed to seek earlier medical attention if their condition changes, for instance if there is pain or growth of a known lesion [61]. It is important to realise that no new osteochondromas develop after puberty. Moreover, regular follow-up to discover potential malignant transformation at an early stage to enable adequate treatment should be considered. The risk of malignant transformation of osteochondroma towards secondary peripheral chondrosarcoma is estimated at 1–5% [2,4,5,13,14,34]. After skeletal maturation a base-line bone scan is recommended [61]. Furthermore, baseline plain radiographs of areas that can not be manually examined, like the chest, pelvis and scapula can be performed [61]. After the base-line documentation one should consider screening patients regularly, for instance every year or every other year. There are as yet no studies available that have proven efficacy of screening. If lesions

change over time, further examination, using magnetic resonance (MR) imaging including contrast enhanced MR sequences, is indicated [61].

In case of malignancy, *en-bloc* resection of the lesion and its pseudocapsule with tumour-free margins, preferably in a bone tumour referral centre, should be performed, resulting in excellent long term clinical and local results. The most common location is however the pelvis where the large cartilage cap can be difficult to excise. In a series of 61 patients with grade I or II secondary peripheral chondrosarcoma of the pelvis published by Donati *et al.*, a 3% local recurrence rate was found after wide resection, in contrast with 23% after inadequate excision [85].

### Prognosis

Osteochondromas are benign lesions and do not affect life expectancy. The risk of malignant transformation is 1–5%. The prognosis for secondary peripheral chondrosarcoma is depending on histological grade: 10 year survival rates are 83% for grade I chondrosarcomas compared to 29% for grade III chondrosarcomas [86].

### Unresolved questions

- How can the enormous difference in disease severity within and between families be explained?
- What drives malignant transformation of osteochondroma and can this be prevented?
- What is the role of EXT in normal cartilage growth and differentiation and in osteochondroma formation?

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## **Additional Resources**

American Academy of Orthopaedic Surgeons Doctor Directory "AAOS"

<http://www6.aaos.org/about/public/members.cfm>

American Association for Hand Surgery "AAHS"

<http://www.handsurgery.org/>

American Society of Anesthesiologists "ASA" "When Your Child Needs Anesthesia"

<http://www.asahq.org/patientEducation/childanes.htm#given>

American Physical Therapy Association "APTA"

<http://www.apta.org/AM/Template.cfm?Section=Home>

Directory listing of Sarcoma Centers

[http://www.mheresearchfoundation.org/Find\\_Sarcoma\\_Centers\\_Directories.html](http://www.mheresearchfoundation.org/Find_Sarcoma_Centers_Directories.html)

Limb Lengthening and Reconstruction Society Doctor Directory "LLRS"

<http://www.llrs.org/ourmemberpage.htm>

Musculoskeletal Tumor Society Orthopaedic Oncologist Directory

<http://msts.org/find.html>

Pediatric Orthopaedic Society of North America Doctor Directory "POSNA"

<http://www.posna.org/parents/public/memdir.cfm>

Shriners Hospitals for Children

<http://www.shrinershq.org/Hospitals/Main/>

The MHE Research Foundation's website contains additional information concerning all aspects of MHE / MO / HME.

<http://www.mheresearchfoundation.org>

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