IJBPAS, August, 2012, 1(7): 991-1002

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

A CLINICAL CASE STUDY ON PRELIMINARY MORPHOLOGICAL WITH MULTIPLE HEREDITARY EXOSTOSES IN A FAMILY

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ABSTRACT

Multiple Hereditary Exostoses (MHE) is an autosomal dominant skeletal disorder showing cartilage capped outgrowths in areas of actively growing bones. The reported risk of malignant transformation is about 0.2% to 5%. The most common benign bone tumors are the Osteochondromas. About one in six osteochondromas arises within the context of Multiple Hereditary Exostoses. MHE is genetically heterogeneous and three genes ext1, ext2 and ext3 are involved. In this study we have reviewed four generations of a family with 32 living members, of which 13 are diagnosed with multiple exostoses. One had been operated for chondrosarcoma, giving the risk for malignant transformation as high as 7.6%. The clinical and radiological outcome of these 13 HME patients (9 families) was investigated by medical history, clinical examination and radiographs. This study corresponds to data of investigators stating that patients

with multiple heredity exostoses carry a relatively high risk of malignant transformation. These probands should be informed about this possibility and regularly reviewed.

Keywords: Multiple Hereditary Exostoses, Chondrosarcoma, Malignant, ROM, Excrescences

INTRODUCTION

Multiple Heredity Exostosis (MHE) is a heterogeneous autosomal dominant disorder in which the penetrance is from 96% to 100% **[1, 2, 3, 4 & 5]**. Multiple Hereditary Exostoses (MHE) is a rare medical condition in which multiple bony spurs or lumps (also known as exostoses, or Osteochondromas) develop on the bones of affected patient. The synonyms used for the disorder are Multiple Osteochondromas (MO) MIM 133700, Heredity Multiple Exostoses (HME) and Multiple Heredity Exostoses (MHE) **[6]**.

The most common benign bone tumors are the Osteochondromas. About one in six osteochondromas arises within the context of Multiple Ostechondromas (MO, Heredity Multiple Exostoses (HME)) **[6]**. Multiple Osteochondromas (MO) / Multiple Heredity Exostoses (MHE) is an autosomal dominantly inherited disorder in which there are numerous cartilage capped excrescences in areas of actively growing bones. MHE is a heterogeneous skeletal disorder in which the penetrance is from 96% to 100% **[7]**. It is characterized by multiple outgrowing bony tumors capped by cartilage, mostly affecting the metaphyses, but also the juxta-metaphyses of the long bones of the upper and lower limbs **[8, 9 & 10]**. Usually the skull is not involved, while flat bones, vertebrae and the ribs may also be affected. There are numerous cartilage capped protuberances at the juxta-epiphyseal areas of the axial skeleton which are usually detectable before the age of 12 years. The Exostoses grow during the childhood and may cause symptoms as a result of compression of local tissues, deformities and discrepancies of length **[11, 12 & 13]**. Typically they appear in the metaphyseal regions of the distal and proximal tibia, distal femur, proximal humerus and in the pelvis and scapula. The affected individuals tend to be short. Relative shortening of the ulna is common with bowing of the forearm. Distal varus deformity of the femur and valgus deformity of the tibia may occur. With a high inter and intrafamilial variability, clinical expression of MHE is more frequent and severe in males than in females. A serious complication of MHE is

the malignant transformation of an exostosis to chondrosarcoma and rarely to malignancies **[14]**. The prevalence of MHE is estimated at 1:50,000 persons within the general population and seems to be higher in males (males to females' ratio 1.5:1) **[15-19]**. The genetic heterogeneity has been shown by detection of at least three gene loci for MHE at which mutations cause the same or similar clinical phenotypes. These three different loci identified by linkage analyses and positional cloning are: EXT1 (MIM*608177; 8q24.11-q24.13) **[1, 7, 4, 25 & 29]**. The responsible gene for MHE phenotype had been identified at EXT1 and EXT2, namely exostosin 1 and 2 (EXT1, EXT2) **[20-24]** and they belong to a family of predicted tumor suppressor genes while gene at EXT3 has not yet been identified. MHE is genetically heterogeneous as three *EXT* loci have been identified so far. *EXT1* (MIM 133700) has been mapped to chromosome 8q23-24, 5 *EXT2* (MIM 133701) to chromosome 11p11-p12, 6 and *EXT3* (MIM 600209) to chromosome 19p **[25-27]**. MHE can cause pain to people of all ages. To children, this can be especially painful. During exercise, it can cause a lot of pain. MHE is characterized by the growth of cartilage-capped benign bone tumors around areas of active bone growth. MHE can lead to the shortening and bowing of bones; affected individuals often have a short stature. Depending on their location the exostoses can cause the following problems: pain or numbness from nerve compression, vascular compromise, inequality of limb length, irritation of tendon and muscle, as well as a limited range of motion at the joints upon which they encroach. In some patients, HME leads to functional and cosmetic alterations as well as bony deformities (e.g., varus or valgus deviation of the knees, coxa valga). Growth disturbances of the legs (e.g., trumpet-shaped metaphysis), forearms e.g., shortening of the ulna with secondary bowing of the radius and development of a pseudo-Madelung deformity), and hands (e.g., short metacarpal) are frequent manifestations. Exostoses located close to the joints may limit range of motion (ROM) and interfere with growth, therefore leading to small stature. Complications in HME include fractures, bursal irritations, and impingement of adjacent structures (tendons, nerves, vessels) **[28, 29]**. A person with MHE has an increased risk of developing a rare form of bone cancer called chondrosarcoma as an adult. The reported rate of transformation ranges from as low as 0.57% to as high as 8.3% of people with MHE. MHE begins to manifest itself in childhood

and currently has no cure. Surgery, physical therapy and pain management are currently the only options available to HME patients, but success varies from patient to patient and many struggle with pain, fatigue and mobility problems throughout their lives. It is not uncommon for HME patients to undergo numerous surgical procedures throughout their lives to remove painful or deforming exostoses, correct limb length discrepancies or improve range of motion. Based on severity, growth progression, localization of exostoses, and patient's complaints, different treatment options were applied for HME. These include surgical removal of exostoses if the tumor causes pain, interferes with joint or muscle function, compress nerves or vessels, or leads to deformities **[29]**. The range of motion refers to the distance and direction a joint can move to its full potential. Each specific joint has a normal range of motion that is expressed in degrees after being measured with a goniometer which is an instrument that measures angles from axis of the joint.

The purpose of this study was to investigate the probability of occurrence of the disorder in the next generation and to observe the penetrance rate. This study would be indeed an initial step towards understanding the inheritance pattern of the disorder. Also, the clinical studies would highlight the disability percentage of those affected probands depending upon the number of excrescences observed in the patient.

MATERIAL AND METHODS

Multiple Hereditary Exostoses affected patients are identified and their consent form is filled up as per the format and guidelines given by Medical Council of India.

An evaluation proforma is filled by a certified medical practioner wherein details of the patient are filled up and certified by the doctor. The following parameters are recorded and evaluated: patient's age, also age of first clinical manifestation, details of any surgeries (indication, the number and location of previous surgeries) and family history. Clinical examination including registration of all palpable exostoses, measurements of the ROM (Range of Motion) in different joints (shoulder, elbow, wrist, hip, and knee), length of the upper and lower arm as well as of the upper and lower leg (clinical evaluation using a measuring tape). X-rays were analyzed to detect the further palpable exostoses. Based on the details obtained, the pedigree analysis and the distribution of exostoses in different anatomical areas are prepared and tabulated.

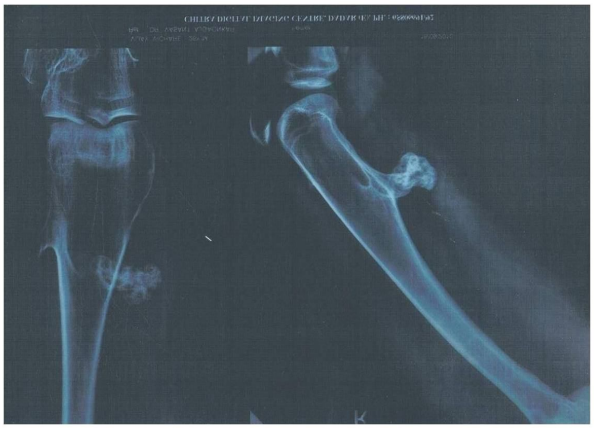


Figure 1: Radiograph Showing Exostoses on Right Femur

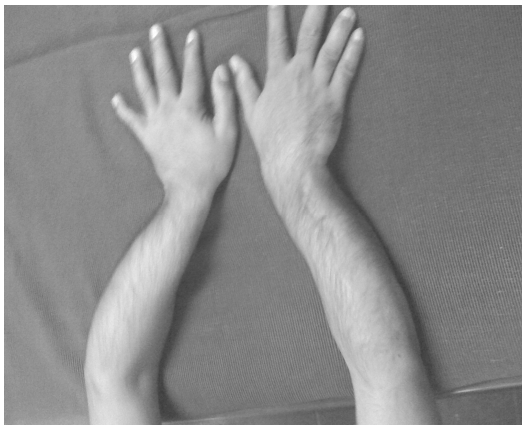


Figure 2: Bowing of Radio Ulna in MHE patient

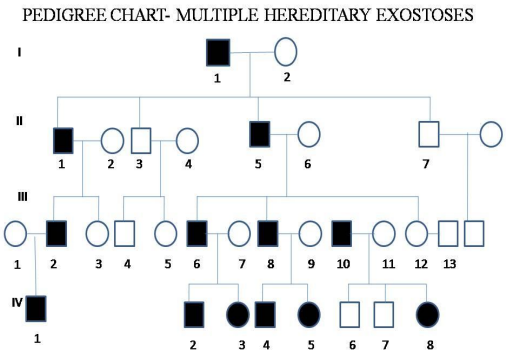
RESULTS AND DISCUSSION

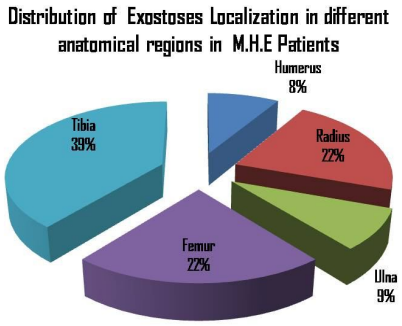
Based on the family history details obtained from the evaluation proforma, the pedigree analysis of the patients is studied and the corresponding pedigree chart is prepared.

The characteristic of pedigree analysis of the family affected with MHE is as follows:

Based on the pedigree chart, the genetic trait observed is autosomal dominant because of the following characteristics: 1. The genetic trait does not skip any generations 2. Affected offspring have an affected parent 3. Unaffected parents do not transmit the trait 4. When one parent is affected and the other parent is unaffected, more than half of the offspring are affected

The probability of the disease occurring in the second generation is 50%; while from second to third generation is 50% and 75% respectively and that in fourth generation is 100%, 100%, 100% and 33.33%. The penetrance probability of the disorder is 100% since in every generation some individuals are affected while expressivity of the disorder is different for different individuals in the family depending upon the percentage of signs and symptoms observed on diagnosis.





In the prospective clinical study, the morphological and functional outcome of 6 HME patients (1 family) was investigated. All the patients analyzed were clinically affected by M.H.E.

Out of 23 evaluated exostoses, 39.13% were located at the Upper half of the body and 60.86% were located at the lower half of the body. Exostoses were found in decreasing numbers in different regions as follows: tibia >femur > radius > Ulna > Humerus. In the present investigation no exostoses were reported in case of clavicle, sternum, hand, fibula and foot. Figure below shows the distribution of exostoses at different anatomic regions in percentages

Range of Motion was affected discusses below: **Case 1- Location of Exostoses with numbers**

Because of presence of exostoses in radial bone, the pronation and supination of the radius was affected by 30^o and 85^o respectively. In case of wrist radial deviation was also restricted. The exostoses at the femur and tibial region affected the flexion and extension of the knees significantly.

Case 2- Location of Exostoses with numbers

The exostoses in the radius bone affected the pronation and supination of the radius by 60^o and 80^o along with restriction in radial and ulna deviation. The external and internal rotation of the hind limbs (femur) was found to be restricted in case of right leg along with restriction observed in dorsiflexion and plantar flexion of the ankle bones. The flexion and extension of the knees were also found to be restricted.

Case 3-Location of Exostoses with numbers

Only one exostoses was reported in the tibial bone of the patient. The exostoses did not affected range of motion in hind limbs.

Case 4- Location of Exostoses with numbers.

Two exostoses were reported at the tibial bone of the patient affecting the flexion and extension of the knee. The dorsiflexion was also found to be restricted.

Case 5- Location of Exostoses with numbers

The shoulder showed terminal restriction bilaterally due to presence of 2 exostoses at the humerus. The flexion and extension of the elbow was affected by 10^{o} respectively. The pronation and supination was affected by 85^{o} and 80^{o} while the flexion and extension of the wrist was affected by 40^{o} and 30^{o} respectively.

Case 6- Location of Exostoses with numbers

The flexion and extension of the elbow was terminally restricted bilaterally. The pronation and supination was affected by 10^{o} and 30^{o} respectively. The exostoses at the hind limbs restricted the flexion and extension of the knees by 90^{o} and the dorsiflexion and plantar flexion of the ankle was also found to be restricted. In our study, the pedigree analysis reveals that the condition has autosomal dominant pattern of inheritance in the family. Also, we found that more number of exostoses are present at the upper half of the body than in lower half. Significant limb shortening is predominant at the upper extremity than in lower ones. We also found that all the affected patients in our study showed a restriction of more than 15^{0} in one or more joints.

COMPARITIVE MASTER CHART OF ANALYSIS

Sr. No	Age	Ht (cms)	Wt (Kgs)	B.M.I	Surgical history in Numbers	Examination of Exostoses on palpation (Total number of Exostoses Present are noted)									
						Sternum	Clavicle	Humerus	Radius	Ulna	Hand	Femur	Tibia	Fibula	Foot
1	26	164	57	21.2	2	**	**	**	1	**	**	2	2	**	**
2	59	156	62	25.5	Nil	**	**	**	2	**	**	1	2	**	**
3	24	149	45	20.3	Nil	**	**	**	**	**	**	**	1	**	**
4	35	157	52	21.1	Nil	**	**	**	**	**	**	**	2	**	**
5	33	150	48	21.3	Nil	**	**	2	1	1		**	1	**	**
6	42	154	47	19.8	Nil	**	**	**	1	1		2	1	**	**

Sr. No	Age	Range of Motion													
		Shoulder						Elbow		Radio Ulna		Wrist			
		Flexion	Extension	Abduction	Adduction	Internal rotation	External Rotation	Flexion	Extension	Pronation	Supination	Flexion	Extension	Ulna Deviation	Radial Deviation
1	26	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	R: 0 - 60° L: 0 - 15°	L: 0 - 60° R: 0 - 5°	Full B/L	Full B/L	Full B/L	Restricted B/L
2	59	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	R: 0 - 30° L: 0 - 15°	L: 0 - 10° R: 0 - 20°	Full B/L	Full B/L	Restricted B/L	Restricted B/L
3	24	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L
4	35	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L
5	33	Terminal Restricted B/L	Terminal Restricted B/L	Terminal RestrictedB/L	Terminal RestrictedB/L	Terminal Restricted B/L	Terminal Restricted B/L	R: 0 - 80° L: 0 - 90°	L: 80 - 0° R: 90 - 0°	R: 0 - 5° L: 0 - 5°	R: 0 - 10° L: 0 - 10°	R: 0 -40° L: 0 - 40°	R: 0 -30° L: 0 - 30°	Restricted B/L	Restricted B/L
6	42	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Terminal Restricted B/L	Terminal Restricted B/L	R: 0 - 80° L: 0 - 70°	R: 0 - 60° L: 0 - 60°	Full B/L	Full B/L	Full B/L	Full B/L

Sr. No	Age	Range of Motion									
		Hind Limbs- Hips						Hind Limbs- Knees		Hind Limbs- Ankle	
		Flexion	Extension	Abduction	Adduction	Internal rotation	External Rotation	Flexion	Extension	Dorsi flexion	Plantar Flexion
1	26	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	R: 0 - 100° L: 0 - 115°	R: 100 - 0° L: 115 - 0°	Restricted B/L	Full B/L
2	59	Full B/L	Full B/L	Full B/L	Full B/L	Restricted @R: Ful @L	Restricted @R: Ful @L	R: 0 - 100° L: 0 - 105°	R: 100 - 0° L: 100 - 0°	Restricted B/L	Restricted B/L
3	24	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L
4	35	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	R: 0 - 85° L: 0 - 100°	R: 85 - 0° L: 100 - 0°	Restricted B/L	Full B/L
5	33	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Restricted B/L	Restricted B/L
6	42	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	Full B/L	R: 0 - 90° L: 0 - 90°	R: 90 - 0° L: 90 - 0°	Restricted B/L	Restricted B/L

CONCLUSION

The penetrance probability of the disorder is 100% since in every generation some individuals are affected while expressivity of the disorder is different for different individuals in the family depending upon the percentage of signs and symptoms observed on diagnosis. The transformation of malignancy may be reported to the severity of the disorder explaining the number of exostoses and the location of the bony outgrowths. It is clarified in our study that the ROM is affected to a larger extent in case of patients showing excrescences at the lower half of the body.

ACKNOWLEDGEMENT

The authors express thank to Dr. Ruturaj Shinde (P.T), Prof. A.N.Kutty, Vice Principal, Pillai's College of Arts Commerce and Science, and all the faculty members from

Department of Biotechnology, Pillai's College, for their valuable time and support extended for completing the study.

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