Multiple Heriditary Exostoses in a Family for Three Generation of Indian Origin with Review of Literature

KALYANI R[1], PRABHAKAR K[2], GOPINATH B[3], SHEIK NASEER B[4], KRISHNAMURTHY DS[5]

ABSTRACT

Multiple hereditary exostoses (MHE) are an autosomal dominant disorder, consisting of multiple cartilage capped bone tumour arising from the metaphysis of long tubular bones. Mutations are seen in Exostosin-1 and Exostosin-2 genes. We present a family of MHE for three generations. The index case was a 10-year-old male presented with multiple exostoses in hand, forearm, leg, right knee and chest. Family history revealed similar complaints in younger brother, father, paternal uncle, paternal aunt & her daughter and grandfather.

Keywords: Exostoses, India, Multiple hereditary exostoses

CASE REPORT

Ten year male, the index case, complained of multiple, painless swelling in forearm, chest, back, ribs, leg and right knee [Table/Fig-1] since four years, gradually increasing in size. Consent for examination and investigation was taken from the parents of the patient and ethical clearance approval was given by the Institutional ethical clearance committee. General examination of index case showed multiple bony swelling over clavicle, ribs, scapula, forearm, around knee joint and ankle joint. Systemic examination, hematological and biochemical investigations were within normal limits. Radiological investigation showed multiple exostoses around knee joint, ankle joint [Table/Fig-2], right clavicle, scapula and calcaneus. Surgical excision of exostoses around knee joint, forearm and chest was done. Grossly specimen showed multiple linear bony fragments, each measuring approximately 1-2 cms in length with one end showing cartilaginous cap. Microscopy showed well formed bony trabeculae with one end having benign cartilage; features were consistent with osteochondroma [Table/Fig-2].

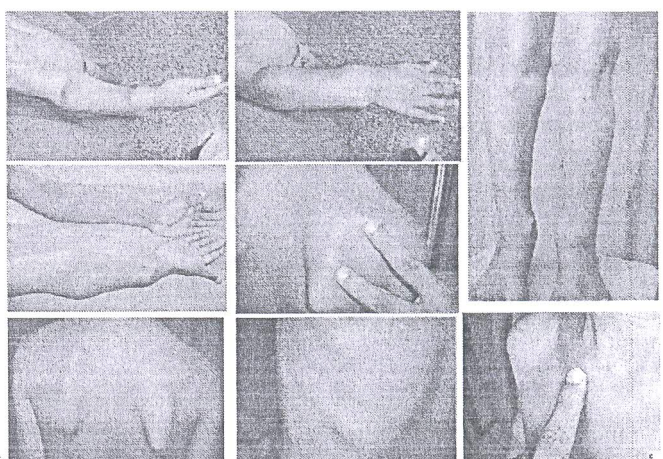
Past history was not significant. Family history revealed similar complaints in grandfather, father, paternal uncle [Table/Fig-3,4], paternal aunt and her daughter and younger brother [Table/Fig-5,6]. Radiological investigations of the affected family members were not done. None of the affected family members had any complications except for bony deformities. Index case, younger brother and grandfather showed normal karyotype. A final diagnosis of Hereditary Multiple Exostoses was made.

DISCUSSION

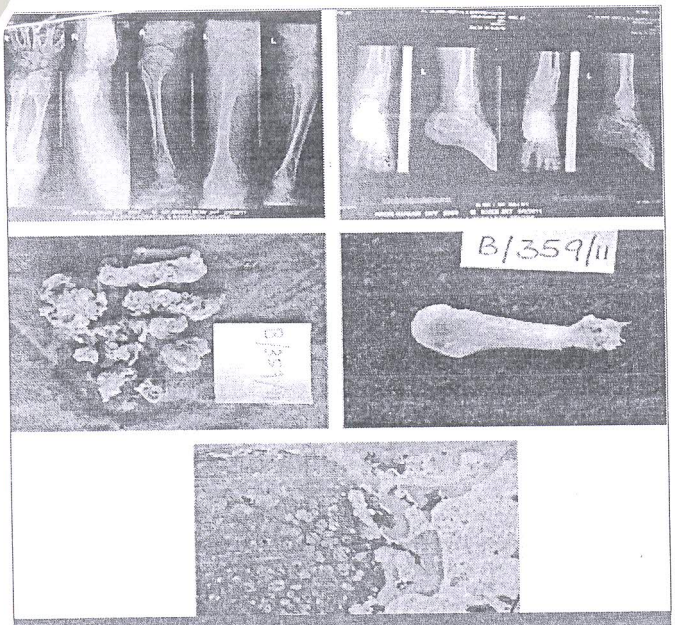
Multiple hereditary exostoses (MHE) is an autosomal dominant benign bone tumour characterized by the formation of multiple cartilage capped bone tumours arising from the metaphysis of long tubular bones [1-4]. It is also called as Hereditary multiple exostoses, multiple osteochrondromatosis and Diaphyseal aclasis. The first description of MHE was given in 1786 [5]. The prevalence of MHE is 1 in 50,000 in general population. However, in Indian population it is very rare [6]. Many cases are under-diagnosed because of mild symptoms and often not identified. MHE accounts for 50% of all surgically treated primary benign bone tumours. 15% of the exostoses are multiple and 62% cases have family history. The solitary form (sporadic form) is approximately 6 times more common than the MHE. Male to female ratio is 1:5:1 with male preponderance because of incomplete penetrance in females and also the fact that females tend to have milder phenotype, hence easily overlooked [2].

MHE is genetically heterogeneous with 96-100% penetrance. The genetic changes are in the cartilaginous cap while the stalk is reactive. 90% of MHE is associated with mutations in tumour genes exostosin 1 (EXT1) and exostosin 2 (EXT 2). Mutation in short arm of chromosome 19, exostoses 3 (EXT3) is suspected. Approximately 10% of cases have de novo mutations. EXT1 and EXT2 gene are tumour suppressor genes involved in heparin sulphate synthesis located in 8q24.11- q24.13 and 11p12-q11 respectively. EXT1 mutation is reported in 22% of sporadic cases and 78% of familial cases. EXT2 is seen in 13% of sporadic cases and 87% of familial cases. In Chinese EXT2 mutations are more common than EXT1. In Caucasians and Asians mutation of EXT1 and EXT2 are reported. Mutations result in increased aberrant chondrocyte proliferation and decreased differentiation associated with disturbed enchondral bone formation giving rise to exostoses. Mutations in EXT1 gene is associated with severe phenotype of the disease and high risk of malignant transformation which follows Knudson's two hit hypothesis [1-4,6]. MHE in two families of Indian origin is reported in which one family had mutations of EXT1 gene and other in EXT2 gene [7]. In the present case only karyotyping was done which was normal.

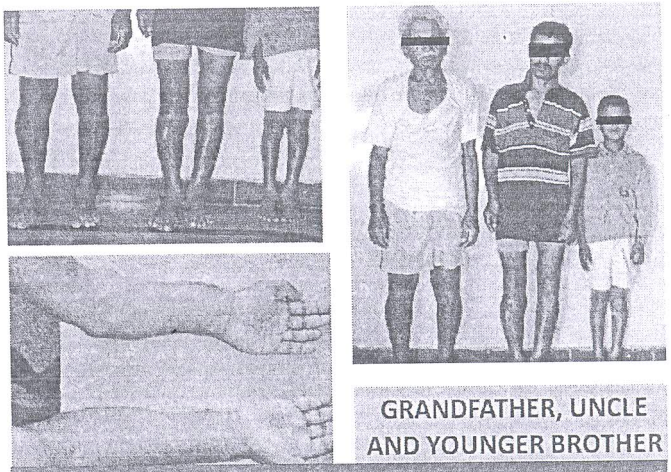
Exostoses are seen in all bones except calvaria of skull, mandible and facial bones which are formed by intramembranous ossification [4]. The common sites are distal femur (90%), proximal tibia



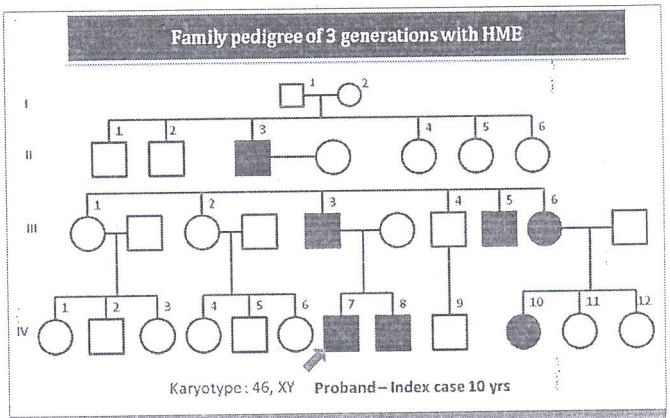
[Table/Fig-1]: Photograph of index case showing the deformity of shoulder, elbow, wrist, knee, ankle joint, right and left scapula, ribs on right side



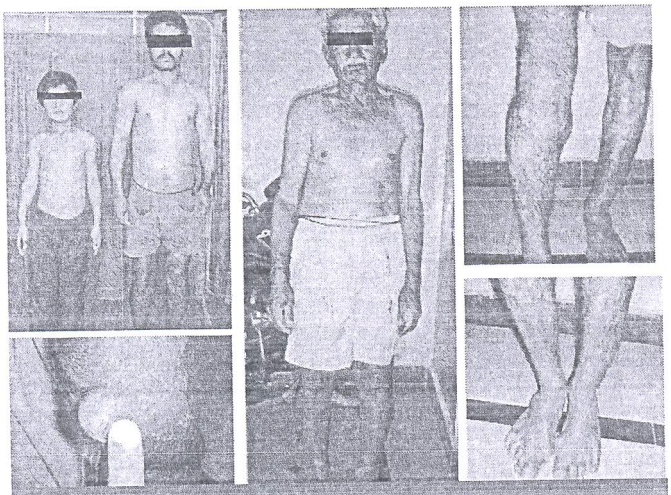
[Table/Fig-2]: X-ray photograph showing exostoses at knee and ankle joint. Gross photograph of one excised exostoses showing linear bone with cartilage cap and multiple excised exostoses. Microphotograph showing well formed bony trabeculae with benign cartilage



[Table/Fig-4]: Photograph of grandfather, paternal uncle and younger brother of index case showing deformity in knee joint with multiple exostoses



[Table/Fig-5]: Family pedigree of 3 generations with MHE



[Table/Fig-3]: Photograph of index case with father, grandfather showing deformity in knee joint, shoulder and elbow joint

present case, the index case and paternal uncle had exostoses in long bones and also in scapula, ribs and calcaneus. The number, size and location of exostoses vary from a few to thousands of exostoses between and within families [1]. Most of the solitary exostoses are non-hereditary and 15% of multiple exostoses occur in context with MHE [2]. The number of locations reported in MHE is 15-18 [3]. All these features were observed in the present case.

Microscopically cartilaginous cap is similar to epiphyseal growth plate having chondrocytes with single nuclei. Binucleated

Clinical Features	II -3 Grandfather	III – 4 Father	III – 5 P Uncle	III – 6 P Aunt	IV – 7 Index case	IV -8 Younger brother	IV-10 Aunt's daughter
Age in yrs	65	40	35	30	10	06	08
Exostosis	Multiple; around knee joints, ankle joint, elbow joint.	Multiple; knee jts, elbow jts, forearm and left scapula	Multiple; knee jts, elbow jts, ankle jts and left scapula	Multiple; around knee jt.	Multiple; knee jts, elbow jts, ankle jts, both scapula, clavicle and ribs	Small around knee jt	Small around knee jt
Deformity	Knee jt	Knee and elbow jt	Knee elbow and ankle jt	Knee jt	Knee, elbow and ankle jt	Knee jt	Knee jt
Surgical excision	No	Done	No	No	Done	No	No
Malignant degeneration	No	No	No	No	No	No	No
Karyotyping	Normal	----	----	-----	Normal	Normal	---

[Table/Fig-6]: Clinical presentation in family members of 3 generations

(84%), fibula (76%) and humerus (72%) i.e. bones that develop from cartilage [1,2]. The flat bones like iliac and scapula are less frequently involved [3]. Rarely ribs, spine, metatarsals, metacarpals, phalanges are involved. Tarsal and carpal bones are not affected except calcaneus occasionally [4]. Vertebral column is involved in 7-9% of cases of which 50% arise from cervical spine [8]. In the

chondrocytes may be seen during active growth. Stalk many times undergoes fracture and hence has reactive fibroblastic proliferation with new bone formation [1]. In the present case the histopathology of excised specimen of index case showed mature bony trabeculae with benign cartilage.

The exostoses usually presents as painless mass at the age of 4-5 y which is usually bilateral, 40% seen before 10 y of age. Usually it remains asymptomatic or present as limb deformity because of skeletal dysplasia or result of local effects on adjacent growth plate[3]. The other complications are compression effects, vascular complications, neural complication and malignant transformation [4]. Malignant transformation is seen in 10% cases of solitary exostosis and 0.5-5% cases of MHE. Secondary peripheral low grade chondrosarcoma (grade II) arising from cartilagenous cap is common and has relatively bad prognosis. Dedifferentiated (High grade) peripheral chondrosarcoma is extremely rare. Oseosarcoma and spindle cell sarcoma arise from stalk in 6% cases. Axial sites as ribs, spine, pelvic hips and shoulder are sites of increased risk of malignant transformation. Average age at malignant transformation in MHE is 25-30 y and for solitary exostoses is 50-55 y. It is rare before 20 y of age [1,3-5]. In the present case, the index case presented at the age of six years. The index case and the affected family members had only bony deformities.

The cartilaginous cap thickness should not be more than 3cms before skeletal maturity and not more than 1.5cms in adults. Growth of exostoses especially after skeletal maturation, increasing pain, irregular mineralization and high thickness of cartilaginous cap (>1-2cm) by x-ray and homogenous/inhomogeneous enhancement of cartilaginous cap by MRI are clue for malignant transformation [1,2]. Cytogenetic studies helps in antenatal diagnosis and counseling the family because the affected individual has 50% risk of transmitting the disorder to their offspring [1,4]. If mutation of EXT gene is not detected, MHE cannot be ruled out because of technical limitations.

The differential diagnoses of MHE are metachondromatosis, dysplasia, epiphysalis hemimelia, Ollier disease, Maffucci syndrome, Langer Giedion syndrome and Patocki-Shaffee syndrome [1,3,5].

MHE does not affect life span or intellect of the person, but should be followed up for early detection of malignant transformation.

To conclude, very few cases of MHE are reported in Indian population. Hence we have reported this case with the intension that it contributes to the medical literature.

REFERENCES

[1] Hameetman L, Bovee JVMG, Taminiau AHM, Kroon MH, Hongendoorn PCW. Multiple Osteochondromas: Clinicopathological and Genetic Spectrum and Suggestions for Clinical Management. *Hereditary Cancer in Clinical Practice.* 2004; 2(4):161-73.

[2] Ivy Jenners, Elena Pedrini, Monia Zuntini, et al. Mutiple Osteochondromas: Mutation Update and Description of the Multiple Osteochondromas Mutation Database. *Human Mutation*. 2009;30(12):1620-27.

[3] Judith VMG Bovee. Multiple osteochondromas. *Orphanet Journal of Rare Diseases*. 2008;3(3):doi:10.1186/1750-1172-3-3.

[4] Pannier S, Legeal-Mallet L. Hereditary multiple exostoses and enchondromatosis. *Best Practice & Research Clinical Rheumatology*. 2008;22(1):45-54.

[5] Hemalatha Anantharamaiah, Kalyani R, Harendra Kumar ML, Manohar PV. Secondary Chondrosarcoma of the lumbosacral Region: Are any bones spared in the Multiple Hereditary Exostoses? *Journal of Clinical and Diagnostic Research*. 2012; 6(10):1778-80.

[6] Vichare VV, Gangawane AR. Multiple Hereditary Exostoses – A Case Report. *IJRRPAS*. 2012;2(5):891-98.

[7] Vanita V, Sperling K, Sandhu HS, Sandhu PS, Singh JR. Novel EXT1 and EXT2 mutations in hereditary multiple exostoses families of Indian origin. *Genet test Mol Biomarkers*. 2009;13(1):43-49.

[8] In-Ho Han, Sung-Uk Kuh. Cervical Osteochondroma presenting as Brown-Sequard syndrome in a child with Hereditary Multiple Exostosis. *J Korean Neurosurg Soc*. 2009;45:309-11.

PARTICULARS OF CONTRIBUTORS:

1. Professor, Department of Pathology, Sri Devaraj Urs Medical College, Sri Devaraj Urs Academy of Higher Education and Research, Kolar, Karnataka, India.
2. Professor, Department of Pathology, Sri Devaraj Urs Medical College, Sri Devaraj Urs Academy of Higher Education and Research, Kolar, Karnataka, India.
3. Resident, Deparment of Medicine, Department of Pathology, Sri Devaraj Urs Medical College, Sri Devaraj Urs Academy of Higher Education and Research, Kolar, Karnataka, India.
4. Professor of Orthopaedics, Department of Orthopaedics, Sri Devaraj Urs Medical College, Sri Devaraj Urs Academy of Higher Education and Research, Kolar, Karnataka, India.
5. Scientific Adviser, Genome Lab, Genome Lab, Sri Devaraj Urs Medical College, Sri Devaraj Urs Academy of Higher Education and Research, Kolar, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Kalyani. R.,
Department of Pathology, Sri Devaraj Urs Medical College,
Sri Devaraj Urs Academy of Higher Education and Research, Kolar, Karnataka, India.
Phone : 9448402775, E-mail : drkalyanir@rediffmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Dec 13, 2013**
Date of Peer Review: **Jul 02, 2014**
Date of Acceptance: **Jul 14, 2014**
Date of Publishing: **Oct 20, 2014**