

## MULTIPLE HEREDITARY EXOSTOSES - CLINICAL FEATURES AND MANAGEMENT

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### Abstract

Multiple hereditary exostoses (MHE) or Multiple osteochondromas is a rare autosomal dominant condition characterized by bony outgrowths (benign tumors) covered by a cartilaginous cap on the outer surface of bone. The prevalence is estimated at 1: 50.000. The syndrome is caused by mutations in members of the EXT gene family, EXT1 or EXT2. The disease is characterized by bone pain, bony deformity and restricted joint motion. We report two cases of skeletally immature patients who presented with multiple exostoses, bone deformation without bone pain; and growth and pubertal retardation. The cases need adequate counseling, long-term follow-up, and measures to improve the quality of life of patients with multiple hereditary exostoses. Multiple hereditary exostoses are rare conditions, and expertise in management of MHE is equally scarce.

**Key words:** Multiple osteochondromas, exostoses, bony deformity

### Introduction

Multiple hereditary exostoses (MHE) or Multiple Osteochondromas is a rare autosomal dominant condition characterized by bony outgrowths (benign tumors) covered by a cartilaginous cap on the outer surface of bone. This tumor develops during childhood or adolescence around the growth plates and it also may develop as a single tumor (osteochondrocartilaginous exostosis). The prevalence is estimated at 1: 50.000, and it seems to be higher in males (male-to-female ratio 1.5:1) (1). In almost 90% of MHE patients germline mutations in the tumor suppressor genes EXT1 or EXT2 are found. However, 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% (2,3). The EXT genes encode glycosyltransferases, catalyzing heparan sulphate polymerization. The pathogenesis of osteochondromas still needs to be elucidated. Osteochondromas develop and

increase in size in the first decade of life, ceasing to grow when the growth plates close at puberty (4). The majority are asymptomatic and located in bones that develop from cartilage, especially the long bones of the extremities, predominantly around the knee (5). The facial bones are not affected. Osteochondromas may be associated with a reduction in skeletal growth, bony deformity, restricted joint motion, shortened stature, premature osteoarthritis, and compression of peripheral nerves (4,5). The risk for malignant degeneration to osteochondrosarcoma increases with age, although the lifetime risk of malignant degeneration is low: 0.57% to 5%, but is rare at children. Being benign lesions and not affecting life expectancy, in most cases, treatment consists of careful observation over time with regular x-rays to keep track of any changes in the tumors but osteochondromas can be surgically removed for cosmetic or functional reasons (6).

### Case report

We report 2 children from nonconsanguineous young parents (under 30 years at the moment of conception). The children were placed in management for basic medical care with the general practitioner. B.A., a 11 years old girl and B.G., a 15 years old boy, were first presented to a geneticists at this age, at the recommendation of the orthopedist. They both presented multiple exostoses starting with the age of 5 years and short stature. However, the sole complaints of patients regarding these tumors were aesthetics and a slight difficulty in walking for the girl.

The mother has a height of 168 cm - 75<sup>th</sup> percentile for height and she is overweight BMI=28.3kg/m<sup>2</sup>. She presents multiple osteochondromas with different locations: curved right second finger, exostose on the distal 1/3 of right radius and on the proximal 1/3 of the left tibia (figure 1).

The father is healthy, with a height of 165cm- the 15<sup>th</sup> percentile for height.

The children's expected height is at 45<sup>th</sup> percentile for age and gender. Expected height for BA at age 11 is 139 cm, while for BG at age 15 years is 165 cm.

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Figure 1. Multiple osteochondromas in the mother.

The genetic pedigree of the family is presented in figure 2, showing strong family determination, several affected individuals occurring in each generation (7). Six males and seven females are affected.

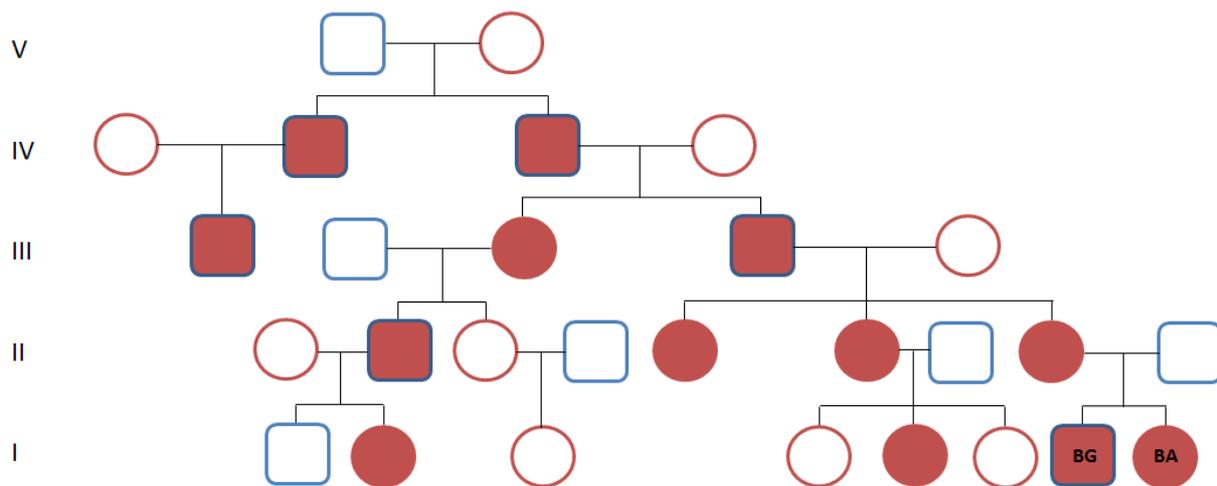


Figure 2. Genetic pedigree. BG and BA are the presented cases.

*The girl*, B.A. at the age of 11, has a height of 134 cm-10<sup>th</sup> percentile for height, weight of 25 kg, BMI=13.96 kg/m<sup>2</sup> – 10<sup>th</sup> percentile. She presents cartilage capped bony outgrowths (osteochondromas) on the distal half of the right forearm, on the proximal finger I and distal finger IV metatarsals, on the proximal left finger II phalanx, finger III with a “mallet finger” aspect, slight varus angulation of the left ankle (figure 3). She presents a slight difficulty in walking. No bone pain was mentioned. Pubertal Tanner stage II. The clinical exam was otherwise normal. She has a normal intelligence and is well integrated in school. The girl is engaged in sports activity in school.

*The boy*, B.G. at the age of 15 has a height of 157cm-3<sup>rd</sup> percentile for height, weight of 42 kg, BMI=17.07kg/m<sup>2</sup> – 10<sup>th</sup> percentile. He presents multiple osteochondromas on the distal half of the ulna and on the proximal half of the radius, curved left forearm, multiples bony growths on the proximal 1/3 of calves, bilateral (figure 4). Pubertal Tanner stage III. No bone pain was mentioned. The clinical exam was otherwise normal. He has a normal intelligence and is well integrated in school. The child is engaged in sports activity in school.



Figure 3. B.A. – female, age 11 years - deformities in hands and right forearm.



Figure 4. B.G. male, age 15 years - Bone deformities in left arm.

Blood work

The usual laboratory investigations (complete blood count, liver and renal function tests, and electrolytes) investigations were unremarkable, with the exception of low serum calcium level. Bone Alkaline Phosphatase and Intact Parathyroid Hormone were in normal range.

Imagistics

Abdominal ultrasound revealed normal aspect. Bone radiographs are illustrated in figures 5 and 6 for B.A. and in figures 7 and 8, for B.G. Head and chest radiographs have normal aspect (not presented), no skull or thorax deformities were observed in both children. The conclusion of the radiologist was: suspected osteogenic hereditary disease.



Figure 5. B.A. Antero-posterior and profile forearm radiographs: Scoliosis in the right forearm bones with profoundly modified radial head by enlarged bulging structure, with growths in the distal half of forearm bones. Changes in the elbow joint axis.



Figure 6. B.A. Antero-posterior left leg: changes in bone structure with bony growths in proximal metatarsals in the finger I and distal finger IV, proximal phalanx left finger II. Fingers III and IV have a “hammer” appearance; proximal phalanges of finger V have a widening shaft.



Figure 7. B.G. Forearm radiography. Left forearm: Cubitus with retarded growth, bony growths in the inferior half of cubitus and proximal half of radius, with curving of radius. Right forearm: Bone node in the distal third of radius and cubitus, with modified contour and shape.



Figure 8. B.G. Feet radiography. Right foot: Inferior tibio-peroneal sinostosis, deformity of metatarsi bones.

We investigated the health-related quality of life (HRQL) in both patients and parents (table 1). There is clearly no impact on the quality of life in children. Overall, the family is not influenced by the existence of this pathology and no difference exists between the perspectives

of the affected parent compared to the healthy one, regarding the functioning of their children. Moreover, due to the fact that they have many relatives with the same condition, they understand the prognosis of the syndrome very well.

Table 1. HRQL in patients and parents perspective.

HRQL	BA	BG
Physical Functioning Scale	99 no impact	90 no impact
Physosocial Health Summary Score	88	84
Father's perspective Physical Functioning Scale	90.6 no impact	87 no impact
Father's perspective Physosocial Health Summary Score	82	80
Mother's perspective Physical Functioning Scale	87 no impact	85 no impact
Mother's perspective Physosocial Health Summary Score	80	79
Family Functioning Father's perspective	98	
Family Functioning Mother's perspective	93	

*The diagnosis* was made on patient history and family history, clinical aspect, lab work and radiological documentation. Screening for germline mutations in *EXT1* or *EXT2* was not performed due to limited resources.

*Management:* The children receive calcium and vitamin D supplements. Surgical intervention was not considered to be appropriate at this stage. As all tumours were identified, the patients were instructed to seek earlier medical attention if their condition changes, for instance if there is pain or growth of a known lesion. Also, they will remain in regular follow-up to discover potential malignant

transformation at an early stage and thus, to enable adequate treatment.

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

#### Discussions

Both children present growth retardation together with pubertal retardation. This is not uncommon in patients with

MHE, especially before puberty (8,9). Clement et al reported that MHE is associated with a diminished stature. Adults with MHE were significantly shorter when compared with a control group ( $P < 0.001$ ); preadolescents, however, were significantly taller than predicted ( $P = 0.01$ ). This was reflected by their height centile; 58% of the adults were under the 25th centile, whereas 53% of the preadolescence group were above the 75th centile. Stature was more severely affected in patients with an EXT1 mutation ( $P = 0.008$ ). This study illustrates a novel age-related growth pattern associated with MHE, which is also affected by genotype (8).

Even though the diagnosis in our cases was clinical, in the case of a positive family history in which MHE is clearly established in relatives, the diagnosis can be clinically made and mutation analysis is not essential (4). Differential diagnosis should be made with Dysplasia Epiphysealis Hemimelica (Trevor's disease, tarso-epiphyseal aclasis) and metachondromatosis are considered in the differential diagnosis of solitary and hereditary osteochondromas. Despite their similarities, they were shown to be separate entities and the EXT downstream pathway is not involved (10). Moreover, MHE 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 (11).

The children presented above did not report bone pain, only small inconvenience at palpation of exostosis, however it does not influence their quality of life. Nevertheless, in literature, the study by Goud et al. showed that approximately 60% of the children had pain (usually associated with a more negative perception of their disease), problems at school, and a greater number of surgical procedures (12). Darilek et al. showed in their cross-sectional study that the prevalence of pain (diffuse, not necessarily over an exostosis) in children and adults with multiple hereditary exostoses reached approximately 80%.

Also, approximately 80% of the patients in their study needed surgical treatment. Over 70% of the study cohort used some pain medication (13).

Surgical management of forearm deformities remains controversial. In a retrospective series 23 MHE patients corrective osteotomy and/or lengthening of forearm bones was not beneficial (14). Moreover, one should consider the possible recurrence of ulnar shortening within 1.5 years when operating skeletally immature patients (14,15). The most beneficial procedure was excision of the osteochondromas. The simple removal of an osteochondroma can improve forearm rotation and correct deformity, especially if there is an isolated tumour of the distal part of the ulna.

Regular follow-up to discover potential malignant transformation at an early stage is very important. The risk of malignant transformation of osteochondroma towards secondary peripheral chondrosarcoma is estimated at 1–5% (16). It is important to realise that no new osteochondromas develop after puberty (4). After skeletal maturation a baseline bone scan is recommended. If lesions change over time, further examination, using magnetic resonance imaging including contrast enhanced magnetic resonance sequences, is indicated.

Consent: Children's legal guardians gave their informed consent to participate in this study.

#### Conclusion

Multiple hereditary exostoses are rare conditions, and thus, expertise in management of MHE is equally scarce. While multiple hereditary exostoses may be seen as a disease of the growing skeleton, it is evident that the burden of this condition extends beyond childhood and adolescence, and this burden may actually worsen throughout life. The cases need adequate counseling, long-term follow-up, and measures to improve the quality of life of patients with multiple hereditary exostoses.

#### References

- Schmale GA, Conrad EU 3rd, Raskind WH. The natural history of hereditary multiple exostoses. *J Bone Joint Surg Am.* 1994 Jul;76(7):986–92.
- Vink GR, White SJ, Gabelic S, Hogendoorn PCW, Breuning MH, Bakker E. Mutation screening of EXT1 and EXT2 by direct sequence analysis and MLPA in patients with multiple osteochondromas: splice site mutations and exonic deletions account for more than half of the mutations. *Eur. J. Hum. Genet.* 2005 Apr;13(4):470–4.
- Jennes I, Pedrini E, Zuntini M, Mordenti M, Balkassmi S, Asteggiano CG, et al. Multiple osteochondromas: mutation update and description of the multiple osteochondromas mutation database (MOdb). *Hum. Mutat.* 2009 Dec;30(12):1620–7.
- Bové JV. Multiple osteochondromas. *Orphanet Journal of Rare Diseases.* 2008 Feb 13;3(1):3.
- Hennekam RC. Hereditary multiple exostoses. *J. Med. Genet.* 1991 Apr;28(4):262–6.
- Willms R, Hartwig CH, Böhm P, Sell S. Malignant transformation of a multiple cartilaginous exostosis—a case report. *Int Orthop.* 1997;21(2):133–6.
- Cook A, Raskind W, Blanton SH, Pauli RM, Gregg RG, Francomano CA, et al. Genetic heterogeneity in families with hereditary multiple exostoses. *Am. J. Hum. Genet.* 1993 Jul;53(1):71–9.
- Clement ND, Duckworth AD, Baker ADL, Porter DE. Skeletal growth patterns in hereditary multiple exostoses: a natural history. *J Pediatr Orthop B.* 2012 Mar;21(2):150–4.
- Sauer S, Rösler H. [Disturbed growth in height in multiple cartilaginous exostoses (author's transl)]. *Z Orthop Ihre Grenzgeb.* 1979 Jun;117(3):309–14.
- Glick R, Khaldi L, Ptaszynski K, Steiner GC. Dysplasia epiphysealis hemimelica (Trevor disease): a rare

- developmental disorder of bone mimicking osteochondroma of long bones. *Hum. Pathol.* 2007 Aug;38(8):1265–72.
11. Mertens F, Unni K. Enchondromatosis: Ollier disease and Maffucci syndrome. Pathology and genetics of tumours of soft tissue and bone. Fletcher CDM. IARC Press; 2002. p. 356–7.
12. Goud AL, de Lange J, Scholtes VAB, Bulstra SK, Ham SJ. Pain, physical and social functioning, and quality of life in individuals with multiple hereditary exostoses in the Netherlands: a national cohort study. *J Bone Joint Surg Am.* 2012 Jun 6;94(11):1013–20.
13. Darilek S, Wicklund C, Novy D, Scott A, Gambello M, Johnston D, et al. Hereditary multiple exostosis and pain. *J Pediatr Orthop.* 2005 Jun;25(3):369–76.
14. Akita S, Murase T, Yonenobu K, Shimada K, Masada K, Yoshikawa H. Long-term results of surgery for forearm deformities in patients with multiple cartilaginous exostoses. *J Bone Joint Surg Am.* 2007 Sep;89(9):1993–9.
15. Matsubara H, Tsuchiya H, Sakurakichi K, Yamashiro T, Watanabe K, Tomita K. Correction and lengthening for deformities of the forearm in multiple cartilaginous exostoses. *J Orthop Sci.* 2006 Oct;11(5):459–66.
16. Porter DE, Lonie L, Fraser M, Dobson-Stone C, Porter JR, Monaco AP, et al. Severity of disease and risk of malignant change in hereditary multiple exostoses. A genotype-phenotype study. *J Bone Joint Surg Br.* 2004 Sep;86(7):1041–6.

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