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Lower limb deformities and limb length discrepancies in hereditary multiple exostoses

Alexandre Madoki, Clément Tuerlinckx, Gauthier Rausin, Kevin Guiraud, Pierre-Louis Docquier

From the Cliniques universitaires Saint-Luc, Service d'orthopédie et de traumatologie de l'appareil locomoteur, Brussels, Belgium

There is a high rate of lower limb deformity and limb length discrepancy in patients with hereditary multiple exostoses (HME). The aim of this study was to evaluate the type and frequency of lower limbs axial deviation and limb length discrepancy and the type of exostoses being risk factors for theses deformities. We retrospectively reviewed standing full-length radiograph of 32 HME patients (64 limbs) followed in our institution between October 2009 and December 2020. Patient demographics were recorded. Radiographic analysis of the coronal limb alignment was performed, limb length discrepancy was measured and topography of the exostoses was recorded. We propose a classification of lower legs in 2 groups and 4 types according to the presence and the location of exostoses. In group I, there is an intertibio-fibular exostose with fibular origin at the level of the tibiofibular joints. In type IA, at the level of the distal tibiofibular joint with ascension of the distal fibula; in type IB at the level of the proximal tibiofibular joint with a bracketing effect on the proximal tibia and a lateral slope of the proximal tibial growth plate; the type IC is combining features of both IA and IB. In group II, there is no intertibio-fibular exostose coming from the fibula and no growth abnormality is obvious. A clinically notable lower limb discrepancy (LLD) of ≥2 cm was found in 19% of our patients. Approximately 33% of patients had a knee valgus deformity and 44% had an ankle valgus deformity. The knee valgus deformity was due to fibular growth anomalies and not to distal femur anomalies. The majority of lower legs had fibular growth anomalies (72%) which was a significant risk factor for knee valgus deformity and leg length discrepancy. On the contrary, we found no correlation between number, location and volume of distal femoral exostoses and genu valgum nor leg length discrepancy. Presence of intertibio-fibular exostoses is a risk factor for knee valgus deformity and leg length discrepancy. The presence of these exostoses should lead to a close follow-up of the patient.

Keywords: Hereditary multiple exostoses; knee; ankle; deformity; EXT gene; limb length discrepancy.

■ Alexandre Madoki[1], MD
■ Clément Tuerlinckx[1], MD
■ Gauthier Rausin[1], MD
■ Kevin Guiraud[1], MD
■ Pierre-Louis Docquier[1,2], MD, PhD

[1]*Cliniques universitaires Saint-Luc, Service d'orthopédie et de traumatologie de l'appareil locomoteur, Avenue Hippocrate 10, B-1200 Brussels, Belgium.*

[2]*Université catholique de Louvain, Secteur des Sciences de la Santé, Institut de Recherche Expérimentale et Clinique, Neuro Musculo Skeletal Lab (NMSK), Avenue Mounier 53, B-1200 Brussels, Belgium*

Correspondence: Alexandre Madoki, M.D., Cliniques universitaires Saint-Luc, Service d'orthopédie et de traumatologie de l'appareil locomoteur, Avenue Hippocrate 10, B-1200 Brussels, Belgium.
Email: alexandre.madoki@uclouvain.be

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INTRODUCTION

Hereditary Multiple Exostoses (HME) or Hereditary Multiple Osteochondromas (HMO) also called Bessel-Hagen disease is an autosomal dominant inherited genetic condition characterized by multiple exostoses (or osteochondromas) that can cause cosmetic complaints, pain, deformity and potential malignant degeneration *(1)*. With an estimated incidence of one in 50,000, HME is a rare orphan paediatric disorder but is nevertheless one of the most common inherited musculoskeletal condition *(2)*. Genetic analysis has identified a family of exostosin (EXT) genes that acts to regulate chondrocyte activity and differentiation in bone's growth plate and if mutated can potentially cause exostoses *(3)*. The majority of HME patients have a positive family history while, in 10% of affected individuals, HME is the result of a de novo pathogenic variant *(4, 5)*. Over 90% of HME cases are found to be associated with heterozygous loss of function mutations in EXT1 and EXT2. Patients with mutations of EXT1 are more severely affected *(6)*. Recent reports have documented an almost equal sex ratio but males seem likely to express a more severe phenotype, probably related to later physeal closure or hormonal differences *(6-8)*. HME penetrance is age related, non sex related and almost complete (94%) *(2)*. HME is characterized by a wide clinical intrafamilial and interfamilial variability. Exostoses vary in number and location as well as the functional impairment and degree of orthopedic deformities they cause *(6, 7)*.

Exostoses are the most common benign bone tumours accounting for 20-50% of benign bone tumours and 9% of all bone tumours *(9)*. It is the result of dysplasia of the peripheral aspect of the growth plate. It corresponds to a well differentiated bone growth, that takes the form of a cartilage-capped bony outgrowth on the surface of the bone.

The most common locations of exostoses are long tubular bones. The topography is first metaphyseal and then gradually migrates to the diaphyso-metaphyseal region due to the subsequent growth of the bone.

Although exostoses usually are benign, malignant transformation to chondrosarcoma or rarely other malignant tumours like osteosarcomas is a major complication. It is mainly seen in adults. The reported rate of secondary chondrosarcoma is ranging from 1% to 11% in HME but stays uncertain *(10)*. The rate of malignant transformation falls to less than 1% in sporadic exostoses *(9)*. Malignant transformation is more frequent in proximal femur, proximal humerus, pelvis and scapular exostoses *(11)*. Fei and al. suggest an annual cervical spine to proximal femur MRI screening for all HME patients between age 20 to 40 *(11)*. Jurik and al. propose the screening to be confined to intervals of 2 years and encompass only the truncus, the proximal femur, and the shoulder girdle *(10)*. As a rule, every patient with a new onset of pain near a preexisting exostose should undergo imaging *(9)*. A cartilage cap thickness greater than 3 cm in children or 2 cm in adults indicates the development of secondary chondrosarcoma *(12)*.

Exostoses are rarely evident at birth and symptoms will manifest during growth. The median age at the time of diagnosis is three years (range from birth to twelve years) *(2)*. During the childhood growth period, the exostoses get bigger, become visible and cause complaints. Approximately 75% of affected individuals have a clinically recognizable osseous deformity, most commonly involving the forearm, the ankle and the knee. Forty % have short stature *(2)*. The lower limb is mainly affected by valgus deformity. There is a high rate of knee deformity, with nearly a third of patients developing genu valgum *(13)*. When studied, the anatomical distribution of the lesions shows that the knee is involved in 93% of the cases *(2)* and, the hip in more than 50% of the cases *(14)*. Valgus deformities at the ankle joint are found in 50% of patients *(15)*. Limb-length discrepancy (LLD) is commonly seen in patients with HME. A clinically notable inequality $\geq$2 cm has been reported in 10% to 25% of affected individuals *(1-6, 16)*.

The primary aim of this study was to describe the epidemiology of knee and ankle deformities and LLD in patients with HME. Reports have documented a leading influence of the distal femur and of the fibula in knee and ankle deformities and LLD *(1, 17, 18)*. Our secondary aim was to identify independent predictors of these deformities. If

predictors were found, they could be used to identify patients at risk who need a closer follow-up.

PATIENTS AND METHODS

Patients with HME followed in our institution between October 2009 and December 2020 were included in this study. Only patients with adequate and available standing full-length digital radiographs of the lower limbs were included leaving 32 patients available for this study (64 limbs). There were 15 males and 17 females. 23 patients had serial radiographs and 9 only one. Only the latest radiograph was considered. In case of surgery of the lower limb (exostosectomies, osteotomies or epiphysiodeses), only the radiograph before the surgery was taken into account. Mean age at the time of the latest radiographic evaluation was 12.1 years (range, 4.6 to 32.4 years).

Different angles were measured on both limbs of the latest standing full-length radiograph according to Paley's method: mechanical lateral proximal femoral angle (mLPFA, normal between 85-95°), mechanical lateral distal femoral angle (mLDFA, normal between 85-90°), medial proximal tibial angle (MPTA, normal between 85-90°), lateral distal tibial angle (LDTA, normal between 86-92°). The Hip-Knee-Ankle angle (HKA) and the MAD (mechanical axis deviation) were measured. For MAD the knee joint was divided into zones for classification with the method described by Mielke and Stevens *(19)* (Fig. 1). LLD was measured both at the level of femoral heads and of the pelvis (iliac wings). The number and location of exostoses affecting the distal femur was recorded as well as femoral, tibial and fibular lengths. To measure the fibular shortening, relative fibula-tibial length (F/T) was evaluated.

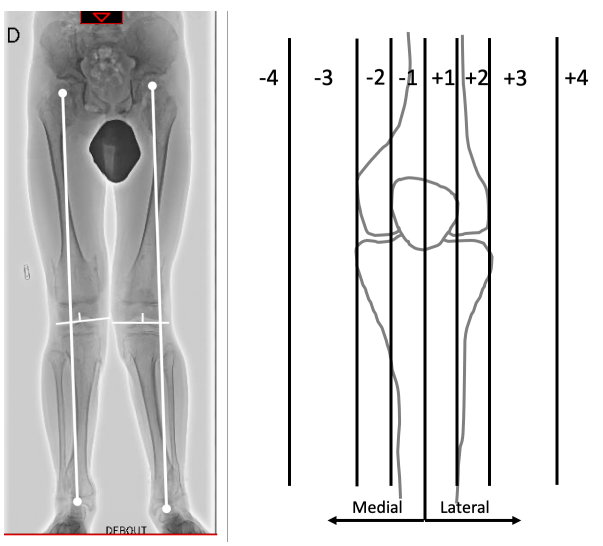

Figure 1. — The knee joint can be divided into four zones with valgus designated as positive and varus designated as negative. The width of zone -1, 1, -2 and 2 are equal to the width of half a tibial plateau. The width of zone −3 and 3 are equal to the width of the medial half of the knee joint. The magnitude of the deformity is classified by determining the zone through which the mechanical axis of the lower limb passes on a weight bearing full-length digital radiograph of the lower limbs.

We developed a classification system for lower limb in four types (Fig. 2). In group I, there was a fibular exostose at the level of the tibiofibular joints: IA, at the level of the distal tibiofibular joint with ascension of the distal fibula; IB, at the level of the proximal tibiofibular joint with a bracketing effect on the proximal tibia and a lateral slope of the proximal tibial growth plate; IC combining features of both IA and IB. In type II, no growth abnormality was obvious despite the possible presence of exostoses.

Four independent observers have classified the 64 lower limbs according to the classification system in order to test the interobserver concordance.

All statistical analyses were performed using IBM SPSS statistics version 27. A Kolmogorov-

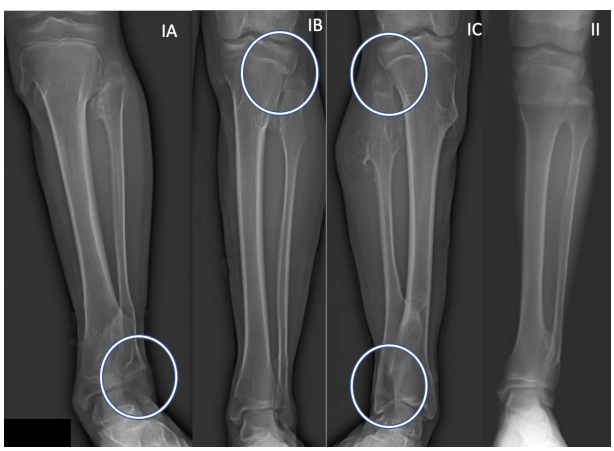

Figure 2. — The knee joint can be divided into four zones with valgus designated as.

Smirnov normality test was used to examine if variables were normally distributed. The p-value of significance was set at $p<0.05$ throughout the study. The Bonferroni correction was used when multiple hypotheses were tested and each individual hypothesis was tested at a significance level of 0.05/m where m is the number of hypotheses.

To test if a mean value was statistically different from 0, a one sample t-test was performed. To compare mean values between the different groups of our classifications, one-way analysis of variance (ANOVA) was performed. To compare mean values between the 2 groups with and without growth anomaly, a multivariate analysis of variance (MANOVA) was performed. To compare categorial data between groups, a Chi-square test was performed. To measure interobserver concordance between the 4 observers, Cohen's kappa coefficient has been calculated.

RESULTS

A familial history was found in 17 patients out of 32 (53%). A short stature (percentile <=10) was found in 32% of the patients. The patients sustained in mean 1 surgery (range, 0 to 8 surgeries). The performed surgery was exostosectomy in 54% of the cases, combined guided growth and exostosectomy in 23%, osteotomy in 15% and guided growth in 8%.

HKA was in mean 2° valgus (range, from 7° varus to 11° valgus) and was significantly different from normal value (0°). There were 37 lower limbs in valgus (58%), 16 with normal axis (25%) and 11 in varus (17%). There was a significative mean LLD: 8mm at the level of femoral heads and 9mm at the level of pelvis. We found significative HKA valgus deformity of 5° or more in 21 cases (33%) and of 10° or more in 3 cases (5%). HKA varus deformity of 5° or more was found in 3 cases (5%) but never more than 10°. We found mean LPFA and mean mLDFA within normal values (Table II) but mean MPTA in valgus and mean LDTA in valgus. Twenty-eight lower limbs (44%) had ankle valgus deformity (LDTA<86°) while 36 others (56%) had no ankle deformity. No ankle varus deformity was found (maximal value was 92° in our series). There was a predominance of MAD in valgus (Fig. 3) (Table I and II).

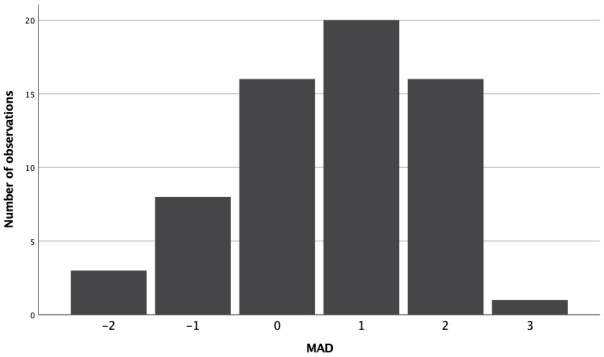

Figure 3. — Graph showing the distribution of MAD. There was a predominance of MAD in valgus.

Table I. — Radiographic measurements

Measures	Mean	minimum	maximum	P value (Different from normal value 0)
HKA (°)	2 (valgus)	-7 (varus)	11° (valgus)	p<0.0001
LLD (mm) (femoral heads)	8	0	26	p<0.0001
LLD (mm) (pelvis)	9	0	28	p<0.0001

Table II. — Radiographic measurements

Angle (°)	Normal values	Mean	minimum	maximum
LPFA (°)	85 to 95	92	87	99
mLDFA (°)	85 to 90	88	81	97
MPTA (°)	85 to 90	92	82	101
LDTA (°)	86 to 92	85	65	92

Agreement was found almost perfect (kappa >0.8) between Observers 1 and 2, while it was found substantial (kappa >0.6) between Observers 1 and 3, between Observers 1 and 4, between Observers 2 and 3 and between Observers 3 and 4 (Table III) ($p<0.001$).

There were more lower limbs with growth anomalies (IA, IB, IC) than without (II) (Table IV).

Table III. — Inter-observer kappa coefficients (p<0.001)

	Observer 2	Observer 3	Observer 4
Observer 1	0.864	0.717	0.669
Observer 2	/	0.700	0.655
Observer 3	/	/	0.759

Table IV. — Classification of lower limbs according to our classification (observer 1)

Type	Frequency
Type IA	18 (28%)
Type IB	9 (14%)
Type IC	19 (30%)
Type II	18 (28%)

By comparison (Table V) between group I (with growth anomalies; Ia, Ib and IC) and group II (without growth anomalies), we found significantly HKA more in valgus, MPTA more in valgus, more LLD and more fibular shortening in group I. mLDFA was found within normal values in both groups. Ankle deformity in valgus (LDTA <86°) was found in both groups.

There were significantly more MAD in valgus in group I than in group II (p=0.046) (Fig. 4).

The mean LDTA was abnormal and in valgus (<86°) in type IA, IC and II while it was found within normal values for type IB but this difference was not significant (Table VI).

Table V. — Comparison between groups with and without growth abnormalities (MANOVA p<0.001)

Radiographic value	Group I (N=46)	Group II (N=18)	P value
HKA	3° valgus	0°	p=0.007
Short stature <P10	33%	32%	NS (p=0.651)
LPFA	93°	92°	NS (p=0.072)
mLDFA	88°	88°	NS (p=0.994)
MPTA	93°	90°	p=0.004
LDTA	85°	85°	NS (p=0.706)
LLD (femoral heads)	11mm	2mm	p<0.0001
LLD (pelvis)	11mm	4mm	p=0.007
Fibular length relative to tibia (F/T)	95%	98%	p<0.0001

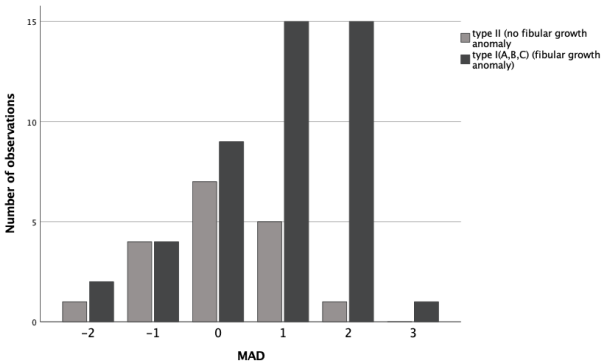

Figure 4. — Chart showing repartition of MAD deviation between the two groups.

Table VI. — Comparison of LDTA between groups

Type	Mean LDTA +/- SD	Ankle in valgus (LDTA <86°)
Type IA (N=18)	84° +/- 4°	10 (56%)
Type IB (N=9)	87° +/- 3°	3 (33%)
Type IC (N=19)	84 +/- 6°	8 (42%)
Type II (N=18)	85° +/- 5°	7 (39%)

Of the affected individuals, 15 were males and 17 females. No significant difference was found between the two sexes (Table VII).

At the level of medial distal femur, there was in mean one exostosis (range, 0 to 3). One medial exostose was found in 63% of the knees while no

Table VII. — Comparison between sex

Radiographic value	Males (N=30 limbs)	Females (N=34 limbs)	P value (Bonferroni correction)
HKA	1.4°	3.4°	NS(P=0.044)
Short stature <P10	5/30	3/34	NS(P=0.221)
MAD -in varus (-1,-2) -neutral 0 -in valgus (+1,+2,+3)	8 7 15	3 9 22	NS(P=0.260)
LPFA	92°	93°	NS(P=0.739)
mLDFA	89°	88°	NS(P=0.260)
MPTA	91°	92°	NS(P=0.280)
LDTA	84°	85°	NS(P=0.039)
LLD (femoral heads)	7mm	9mm	NS(P=0.681)
LLD (pelvis)	8mm	10mm	NS(P=0.572)
Fibular length relative to tibia (F/T)	96%	96%	NS(P=0.479)

medial exostosis in 23%, 2 exostoses in 11% and 3 exostoses in 3%. Voluminous medial exostoses were found in 58% of the knees.

At the level of lateral distal femur, there was in mean one exostosis (range, 0 to 2). One lateral exostose was found in 53% of the knees, while no lateral exostosis in 38% and 2 exostoses in 9%. Voluminous lateral exostoses were found in 31% of the knees.

There was no significant difference for MAD, HKA, LPFA, mLDFA, MPTA, LDTA, F/T and LLD related to the number of exostoses.

Considering potential bracketing effect of an exostosis on distal femur, we found neutral effect (equal presence of voluminous exostosis both medial and lateral) in 73% of the knees, while potential varus effect (presence of voluminous medial exostosis without voluminous lateral exostosis) in 17 knees (27%) and no knee with potential valgus effect (presence of voluminous lateral exostosis without voluminous medial exostosis). There was no significant difference for MAD, HKA, LPFA, mLDFA, MPTA, LDTA, F/T and LLD related to this varus effect. Of the 17 knees with potential varus effect, three knees were found with negative MAD (in varus), five knees with MAD equal to 0 and 9 with positive MAD (in valgus) (non-significant).

Table VIII and Fig. 5 show the distribution of mLDFA related to MPTA. Of the 44 knees with MPTA in valgus, 28 had normal mLDFA and 4 had mLDFA in valgus while we found compensatory effect of the femur in 12 knees (mLDFA in varus). We found poor correlation between mLDFA and MPTA (R2=0.013).

DISCUSSION

A family history was found in 53% of our patients, which corresponds to the rate reported by Pierz et al. (46.5%) (1). The higher rate of Schmale's study (90%) is due to the effort of reaching out all the family members of the families who had a confirmed diagnosis of HME to the scale of a whole state *(2)*.

Table VIII. — Cross tabulation of mLDFA and MPTA

	MPTA in varus (<85°)	Normal MPTA (85 to 90°)	MPTA in valgus (>90°)
mLDFA in varus (>90°)	1	3	12
Normal mLDFA (85 to 90°)	0	12	28
mLDFA in valgus (<85°)	0	4	4

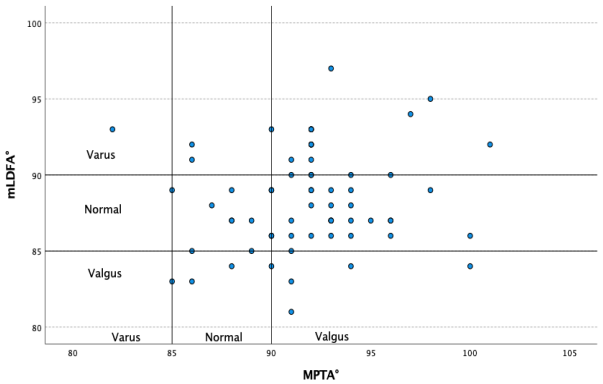

Figure 5. — Scatter plot of mLDFA related to MPTA.

We found short stature in only 32% of our cases but only four of our cases had reached skeletal maturity at the time of the latest radiograph. Clement et al. found that 58% of the HME adults were under P25, whereas 53% of the preadolescence group were above P75 *(21)*. This confirms that the growth loss occurred mainly during the growth spurt of the adolescence and explain the low rate of short stature in our series. Fibular growth abnormalities do not seem to influence stature in the present study, but again short stature should be evaluated after skeletal maturity.

Our study population is meanly paediatric. It could explain the lower rate of 57% of surgical history with an average of one procedure for each patient. Schmale's reported surgical history rate is 74% with an average of 3 procedures *(2)*. The young mean age of our patients could also explain why no malignant degeneration was reported in our series. Ochsner et al. published a report of 59 patients with HME who had malignant degeneration. The mean age of diagnosis of malignancy was 31 years *(20)*.

We found a clinically notable LLD of ≥2 cm in 19% (6/32) of the patient which is consistent with the literature *(1-3, 16)*. The rates of significant knee valgus of 33% and significant ankle valgus of 44% is also consistent with previous series *(2, 1, 13)*. Like proposed by Nawata and Shapiro *(13, 16)*, the

present study shows that knee valgus deformity is to be related to proximal tibial valgus and not to distal femoral valgus as mean HKA was in valgus, mean MPTA was also in valgus (>90°) but mean mLDFA was within normal values (Table II). This observation was even more explicit when the cohort was organised in two groups: with and without fibular growth anomalies (Table V). This would mean that valgus knee deformity is mainly caused by proximal tibial changes that are related to intertibio-fibular exostoses.

Clement and al. showed the influence of the increasing number of distal femoral exostoses on the degree of genu valgum *(17)*. We found no correlation between number, location and volume of distal femoral exostoses and genu valgum nor LLD. The young age of the patients (skeletal maturity not reached), the small number of patients could possibly explain why.

The classification in two groups with and without fibular growth anomalies shows the influence of fibular exostoses on HKA, MPTA, LLD and fibular shortening as we found more valgus HKA, more valgus MPTA, more LLD and more fibular shortening in group I (Table V). Fibular growth anomalies (group I) were indeed very frequent and found in 72% of the case.

Ahn and co proposed a similar classification reviewing 63 patients with HME. They focused on tibiofibular exostoses classifying the lower legs into four groups: A: proximal and distal tibiofibular exostose, B: proximal tibiofibular exostose, C: distal tibiofibular exostose and D: no tibiofibular exostose. Their conclusion is that ankle valgus deformities can be the result not only of distal tibiofibular exostoses but also proximal exostoses *(18)*. The same conclusion cannot be made in the present study about the influence of fibular exostoses on ankle valgus deformity. Among the 64 lower limbs, 28 (44%) had ankle valgus deformity and the mean LDTA was valgus (<86°) but LDTA was not statistically different between group I and II. We think that intertibio-fibular exostoses are leading to differential growth speed between fibula and tibia which generates proximal tibia deviation into valgus and knee valgus deformity. But the lower limbs without evident fibular growth anomaly (group II) also had ankle valgus deformities, which cannot be explained by this phenomenon.

The classification we propose focus on intertibio-fibular exostoses. The interobserver reproducibility was substantial to perfect according to Cohen's interpretation *(22)*.

Pierz demonstrated that the distal femur could in some case complement the proximal tibial deviation to maintain a close to normal mechanical axis *(1)*. We looked for opposing angular knee deformities (high MLDA, high MPTA, normal HKA and oblique articular line) of distal femur and proximal tibia and found only 12 knees showing this pattern. This shows a potential reciprocal influence between distal femur and proximal tibia but not in most of the cases (Table VIII, Fig. 5).

Pedrini and al. demonstrated male gender and EXT determination to be predictors of the clinical and functional severity of HME *(7)*. We found an almost equal male-female ratio *(15-17)* and no radiological difference between the two groups (Table VII). Due to the small number of reported EXT determination (9 patients), no correlation between genotype and the disease severity have been found. The absence of functional evaluation and genetic systematic screening is a limitation of this study.

CONCLUSION

Valgus deformity at the level of the knee and of the ankle is predominant in patients with HME. The occurrence of LLD is higher than in general population. Intertibio-fibular exostoses appears to be an independent predictor of valgus knee deformity and LLD. The leg being constituted by two parallel bones, intertibio-fibular exostoses can shorten the fibula leading to valgus at the level of proximal and distal tibia. In the absence of interetibio-fibular exostoses, no knee valgus deformity is present but ankle valgus deformity can nevertheless occur. The coronal alignment in HME patients should take into account the presence of intertibio-fibular exostoses and the relative fibular shortening compared to tibia.

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