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ORIGINAL ARTICLE

Scoliosis in patients with multiple hereditary exostoses

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Abstract
Purpose To investigate the prevalence of and to identify independent predictors associated with scoliosis in patients with multiple hereditary exostoses (MHE).
Methods Fifty patients with MHE were clinically examined, and the diagnosis of scoliosis was made based on radiographs. To classify disease severity, three classes based on the presence of deformities and functional limitations were defined. Significant independent predictors of scoliosis in MHE were statistically analyzed.
Results Scoliosis was present in 36 patients (MHE-scoliosis) (72 %). In the MHE-scoliosis group, the mean primary curve was 15.3° ± 5.7° (range 10°–34°) and the mean minor curve was 10.6° ± 7° (range 6°–32°). Left curve was predominant (72 %), and the apex was located in the thoracolumbar or lumbar spine in 64 % of patients. Univariable and multivariable analyses confirmed that MHE severity was a significant predictor of moderate scoliosis (≥20°).
Conclusions Our study confirmed that scoliosis is a common feature of MHE and disease severity is a predictor of moderate scoliosis (≥20°).

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Introduction

Multiple hereditary exostoses (MHE), also known as multiple osteochondromatosis, is an autosomal dominant disorder characterized by the formation of multiple cartilage-capped bony protrusions (osteochondromas, OCs). The prevalence of MHE is estimated to be 1 in 5,0000, making it the most common skeletal dysplasia in humans [1]. In patients with MHE, OCs occur in almost all types of bones, including flat bones, ribs, and vertebrae, although they most typically form at the metaphysis of long bones. It is important to distinguish MHE from solitary OC [2]. Genetic linkage analysis has identified two genes that are associated with the vast majority of MHE: *EXT1*, located on chromosome 8q24.1, and *EXT2*, located on chromosome 11p11 [3]. It has been established that *EXT1* and *EXT2* jointly encode a glycosyltransferase essential for heparan sulfate (HS) synthesis [4], and the critical step in the pathogenesis of MHE involves disturbances in HS polymerization [5].

In addition to multiple OCs, MHE patients also have various deformities of the appendicular skeleton [6]. The common deformities in MHE include limb length discrepancy, valgus deformity 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 [7–9].

We previously confirmed, using a HS-deficient mouse model, that skeletal development requires normal expression of HS, namely development of mesenchymal

condensation, digit patterning, and joint development [10]. Given the known role of HS in morphogen binding, it is likely that the absence of HS disrupts some aspects of morphogen signaling that is critical for the developmental processes of the axial skeleton. Meanwhile, one recent study showed that HS had a widespread distribution throughout the developing spine [11], suggesting that MHE patient might have spinal deformities.

Accordingly, scoliosis associated with MHE has been described [12]. However, the exact prevalence of scoliosis in MHE patients remains unclear. In this study, we describe the epidemiology of scoliosis in patients with MHE for the first time and identify independent predictors associated with scoliosis in MHE patients.

Methods

Patients

A clinical diagnosis of MHE was made in 50 patients based on medical history and physical examination by one or more orthopedic surgeons experienced in diagnosing MHE (YM, KM). Demographic details were recorded. The number of palpable OCs was recorded for all patients according to the anatomical location. The number of skeletal sites with OCs was also evaluated, and patients were divided into two groups: those with fewer than five sites and those with five or more sites. Additional clinical data, including the presence of deformities and functional limitations, were collected. For classification of disease severity, a previously validated classification system was used [13]. Briefly, three classes, based on the presence of deformities and functional limitations, were defined (Table 1). Typical skeletal deformities of MHE are shortening of the ulna with secondary bowing of the radius, varus or valgus angulation of the knee, and deformity of the hand [7–9]. Functional limitations were defined as restricted joint motion caused by deformities or functional impairments caused by the presence of OCs.

Table 1 Clinical classification of MHE

I	No deformities and no functional limitations
IA	≤5 sites with osteochondromas
IB	>5 sites with osteochondromas
II	Deformities and no functional limitations
IIA	≤5 sites with deformities
IIB	>5 sites with deformities
III	Deformities and functional limitations
IIIA	Functional limitation of 1 site
IIIB	Functional limitation of >1 site

Diagnosis and analysis of scoliosis

Standing anteroposterior vertebral radiographs consisting of a single full-spine image were prospectively obtained and read by two orthopedic surgeons with experience in spine surgery. These observers were blinded to the patient's clinical data. Coronal vertebral angular measurements were made using Cobb's method [14]. Average values of the measurement of two observers were considered as the final measurement values. The interobserver coefficients of variability for Cobb angle were evaluated, and we found the linear correlations between the measurements (Spearman correlation coefficient; $r = 0.89$). Thus, we considered that the interobserver differences in measurements would not cause the significant adverse effect on the subsequent statistical analysis. Scoliosis was defined as curvature greater than 10°, and curve patterns were described according to King's classification [15]. The Nash and Moe method was used to determine the degree of rotation of the apical vertebra [16].

Statistical analysis

All statistical analyses were performed with the JMP software program (version 9.0.1, SAS Institute). Pearson's or Spearman's rank correlation coefficients were used to assess the relationship between linear variables. Dichotomous variables (sex; number of OCs, dichotomized as less than five sites or more than five sites; limb deformity, malignant transformation, and disease severity) were compared between patients with and without 20° or more than 20° of scoliosis using the Chi-square test, or Fisher's exact test if there were five or fewer subjects in a group. Multivariable logistic regression analysis was used to identify significant independent predictors of scoliosis of 20° or more than 20°. A p value of less than 0.05 was considered statistically significant.

Results

The study cohort consisted of 50 patients (30 males and 20 females) with a mean age of 28.1 years (range 2–77 years, standard deviation (SD) 18.4 years). Nineteen patients had OCs at fewer than 5 sites, and 31 patients had OCs at 5 or more sites. Thirty-seven patients had deformities in their extremities. There were three cases of malignant transformation, all diagnosed as grade I chondrosarcoma. Patients were divided into 3 groups based on MHE severity: 12 patients with class I, 20 with class II, and 18 with class III disease. The details of the patients' demographic and clinical characteristics are summarized in Table 2.

Table 2 Demographic and clinical characteristics of the study patients

Age (years)	28.1 ± 18.4
Sex	
Male	30
Female	20
Number of OCs	
≤5	31
>5	19
Limb deformity	
Present	37
Absent	13
Malignant transformation	
Present	3
Absent	47
Disease severity	
Class I	13
Class II	18
Class III	19

OC osteochondroma

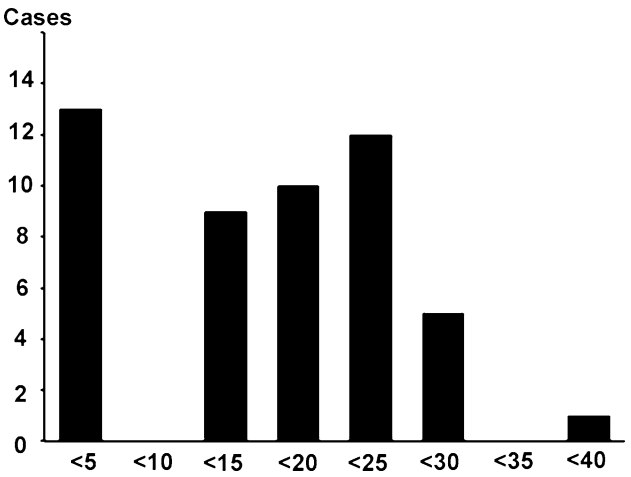

Fig. 1 Distribution of MHE patients according to the angle of scoliosis

Scoliosis was present in 36 patients (MHE-scoliosis) (72 %). No patients were treated with surgery or bracing. In the MHE-scoliosis group, the mean primary curve was 15.3° (range 10°–34°, SD 5.7°) and the mean minor curve was 10.6° (range 6°–32°, SD 7°). The Cobb angle distribution for all the patients is shown in Fig. 1. Ten patients had right scoliosis, and the remaining 26 patients had left scoliosis. The mean number of curved segments was 7.8 vertebrae (range 4–12, SD 2.4). The distribution of the apex is shown in Fig. 2. Regarding curve type, we observed King type I in 10 patients, King type II in 4, King type III in 13, and King type IV in 9. There were no

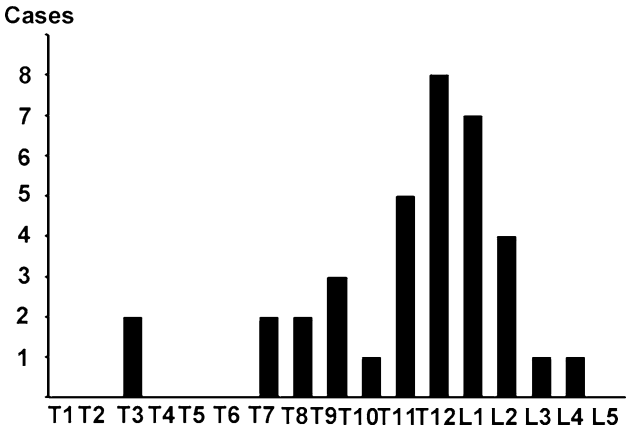

Fig. 2 Distribution of the apex vertebra in MHE patients with scoliosis

patients with King type V scoliosis. The mean Nash and Moe grade of apical vertebra rotation was 2.1 ± 0.8 (SD).

To identify predictors of moderate scoliosis (≥20°), we performed univariable and multivariable analyses, with variables including sex, number of OCs, limb deformity, and disease severity (Class I, II, or III). In the univariable analysis, moderate scoliosis was significantly associated with disease severity (odds ratio [OR] 10.5, 95 % confidence interval [CI] 2.23–77.5, $p = 0.002$) but not with sex, number of OCs, limb deformity, and malignant transformation (Table 3). In addition, multivariable analysis confirmed that disease severity was a significant predictor of moderate scoliosis (OR 10.6, 95 % CI 1.42–225, $p = 0.019$) (Table 3).

Case presentation

A forty-year-old male with MHE had multiple lesions in the upper and lower extremities (Fig. 3a). He also had scoliosis that curved to the left, measuring 22° between L1 and L5 (Fig. 3b). In addition, bilateral coxa valga with bilateral acetabular dysplasia was observed. Both hips were subluxed, and the range of joint motion was limited; thus, he was classified as having class III MHE. He initially underwent a varus proximal femoral osteotomy of his left hip, along with valgus femoral osteotomy on the right (Fig. 3c).

Discussion

This report includes the first systematic examination of the prevalence and severity of scoliosis in a certain number of patients with MHE. The prevalence of scoliosis in normal

Table 3 Predictors of moderate scoliosis (≥20°) based on univariable and multivariable analyses of MHE patients

Characteristic	Scoliosis		Univariable			Multivariable		
	≥20°	<20°	OR	95 % CI	*p* value	OR	95 % CI	*p* value
Sex								
Male	7	23	1.72	0.41–8.9	0.46	1.18	0.19–8.03	0.86
Female	3	17						
Number of OCs								
>5	7	24	1.56	0.37–8.05	0.56	0.73	0.1–5.04	0.74
≤5	3	16						
Limb deformity								
Present	9	28	3.86	0.62–75	0.16	0.95	0.03–25	0.94
Absent	1	12						
Malignant transformation								
Present	0	3	1.1e−8	0–3.6	0.24	1.3e−6	0–33.7	0.54
Absent	10	37						
Disease severity								
I or II	2	29	10.5	2.23–77.5	0.002*	10.6	1.42–225	0.019*
III	8	11						

OR odds ratio, *CI* confidence interval

* Statistically significant

children and adolescents has been estimated to be lower than 2 % [17]. Meanwhile, the prevalence of scoliosis in patients with MHE was as high as 70 %, strongly suggesting a correlation between MHE and scoliosis. Regarding the clinical characteristics of scoliosis in MHE, left curve is predominant (72 %) and the apex was located in thoracolumbar or lumbar spine in 64 % of cases, indicating that the features of scoliosis in MHE are quite different from those in adolescent idiopathic scoliosis. On the other hand, the distribution of King curve type was relatively even. In terms of the progression of scoliosis, we did not observe any significant association between age and severity of scoliosis in MHE; however, a longitudinal cohort study should be conducted to characterize the natural course of scoliosis in MHE.

We recently established a mouse model based on stochastic tissue-specific inactivation of *EXT1* (*EXT1*-SKO mice). Surprisingly, mice with inactivated *EXT1* in a minor fraction of chondrocytes developed multiple OCs and bone deformities in a pattern almost identical to human MHE. The penetrance of the long bone OC phenotype in *EXT1*-SKO mice was 100 %. The bowing deformity of the radius and subluxation or dislocation of the radial head was observed in 91.7 % of *EXT1*-SKO mice, whereas scoliosis was found in 58.3 % [1]. The prevalence of scoliosis in human MHE and *EXT1*-SKO mice was similar. Thus, together with the pattern of OC formation and skeletal defects, we propose that *EXT1*-SKO mice represent a phenocopy of the skeletal defects in MHE and *EXT1* inactivation is associated with the development of scoliosis in MHE patients.

The EXT1 and EXT2 proteins form an oligomeric complex that catalyzes the copolymerization of GlcNAc and GlcA residues, thereby elongating the HS backbone [4]. HS is thought to regulate signaling via a number of HS-binding morphogens and growth factors through diverse, but not mutually exclusive, mechanisms. Conditional ablation of Ext1 and HS synthesis in the appendicular skeleton reveal that HS is essential for normal appendicular skeletal development, especially the development and patterning of mesenchymal condensations. We confirmed that disorganized distribution of bone morphometric protein (BMP), a HS-binding protein, is a critical point of HS involvement in this developmental process [10]. Interestingly, mice lacking both growth/differentiation factors 5 and 6 (*GDF5/6*), a distinct subgroup within the BMP family, show multiple defects, including severe reduction or loss of some skeletal elements in the limbs, altered cartilage in the intervertebral joints of the spinal column, and scoliosis. These results suggest that members of the GDF subgroup are required for normal formation of the axial skeleton and that abnormal distribution of GDF5/6 or malfunction of GDF5/6 signaling may constitute one of the mechanisms underlying the development of scoliosis in MHE [18].

Fibroblast growth factors (FGFs) play important roles in many biological processes, including development, pattern formation, and tissue remodeling. FGFs are involved in all stages of skeletogenesis, from limb bud development to bone growth and remodeling. Notably, FGF receptor type 3 (*FGFR3*)-deficient mice developed scoliosis of varying degrees by the time they reached 3 months of age [19]. HS

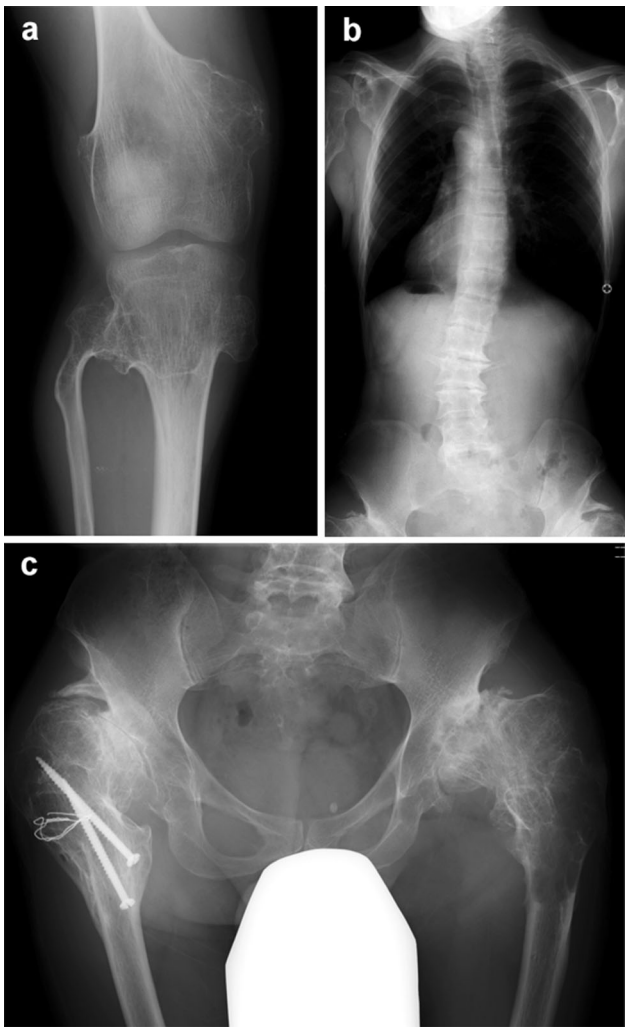

Fig. 3 A 40-year-old male with MHE. **a** Multiple lesions in the lower extremities. **b** Scoliosis with a 22° curve that is convex to the left between L1 and L5. **c** AP pelvic radiograph. The patient initially underwent a varus proximal femoral osteotomy of his left hip, accompanied by right valgus femoral osteotomy for bilateral coxa valga with bilateral acetabular dysplasia

acts as an essential coreceptor in FGF signaling, activating downstream signaling [20]. In addition, recent reports suggest that FGFR3 regulates disk development and ossification of the vertebral bodies [11]. Therefore, disruption of FGFR3 signaling in MHE patients could be another explanation for the development of scoliosis in MHE.

Remarkably, we have recently established the methods for the isolation and the quantitative analysis of HS from plasma and cellular fractions of human blood [21]. By this method, we found that the HS amount in blood samples of MHE patients was reduced and varied among individual patients. Such reduced HS amount in the blood of MHE patients may be due to decreased EXT enzyme activity in MHE patients. Thus, the values of the HS amount in the blood samples would reflect the disease severity of the MHE patients, and we are going to investigate the correlation between the severity of scoliosis and the HS amount in blood samples of MHE patients.

There is a wide distribution in the number of OCs, limb deformities, and malignant transformation among MHE patients. Our study confirmed that scoliosis in MHE is a common feature; however, we were unaware of any published studies identifying independent predictors of scoliosis in MHE. If predictors were identified, they could be used to identify patients at risk of scoliosis for whom treatment during the skeletal growth period may prevent progression of scoliosis. Recently, a clinical classification system for MHE has been developed [13]. In this classification system, MHE is divided into three classes according to the number of bone segments affected and the presence of skeletal deformities and/or functional limitations. This classification has been validated through a Switching Neural Network approach and provides an efficient method to characterize MHE.

Importantly, we found that scoliosis was significantly more common in patients with class III MHE compared to patients with class I and II MHE. This finding suggests that involvement of the spine may occur as part of general disease severities. For this reason, patients with class III disease need to undergo appropriate clinicoradiographic investigation of the spine for scoliosis, such as radiographic examination of the entire spine. Once the diagnosis of scoliosis is made, each individual MHE patient should be closely monitored to evaluate the progression of scoliosis and to establish the feasibility of surgical treatment.

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Conflict of interest None.

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