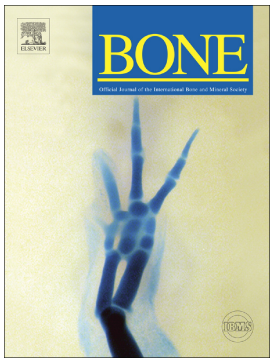

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The Natural History of Multiple Osteochondromas in a Large Italian Cohort of Pediatric Patients

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ABSTRACT

Importance

Multiple osteochondromas is a rare hereditary skeletal disorder, characterized by bony protrusions arising from growth plates on long bones during skeletal development. The disorder frequently leads to diminished stature, deformities and functional limitations. Understanding of the natural history of multiple osteochondromas and its evolution in children and adolescents is limited.

Objective

To provide valuable information on the natural history of multiple osteochondromas, to inform recommendations for treatment and prevent impairments caused by osteochondromas.

Design

This retrospective cohort study in children with multiple osteochondromas includes longitudinal data collected from first to last follow-up visit for patient demographics, and over 36 months for disease evolution.

Setting

Data were collected from the Registry of Multiple Osteochondromas, which includes data from circa 1,200 patients with multiple osteochondromas treated from 2003–2017 at IRCCS Istituto Ortopedico Rizzoli in Bologna.

Participants

Patients ≤18 years with multiple osteochondromas, who provided written informed consent and had data for ≥1 12-month follow-up visit.

Main outcome(s) and measurement(s)

Demographics, clinical features, incidence of surgeries, and disease evolution (progression or regression) were assessed. Results were summarized using descriptive statistics, annual rates of new clinical features and surgeries, and Kaplan-Meier estimates. Patient height was evaluated following Italian growth charts.

Results

158 patients were included in these analyses. Throughout follow-up, 80.4% of patients developed new osteochondromas, 57.6% developed new deformities, 23.4% developed new functional limitation(s). New osteochondroma(s) were developed by 28.5% patients by Month 12, 39.9% at Month 24, 50% at Month 36. Most new osteochondromas were detected in the younger population; patients aged 0–4 years underwent a significantly higher number of lesions within 12, 24 and 36 months of follow-up. The overall incidence of patients with ≥1 new deformity within 12 months was 17.7%, with incidences decreasing with increasing age ($p=0.023$). In addition, the analyses on height highlight that 13 years is a cut off age for slow growth of the stature ($p<0.0005$). At last follow-up visit, 46.2% of patients had disease progression, while regression (spontaneous and surgical) occurred in 7.6% ($p=0.007$).

Conclusions and Relevance

This natural history study reports the main set of clinically relevant data for patients with multiple osteochondromas during skeletal development, providing insight for patient management and development of therapeutic interventions.

Keywords

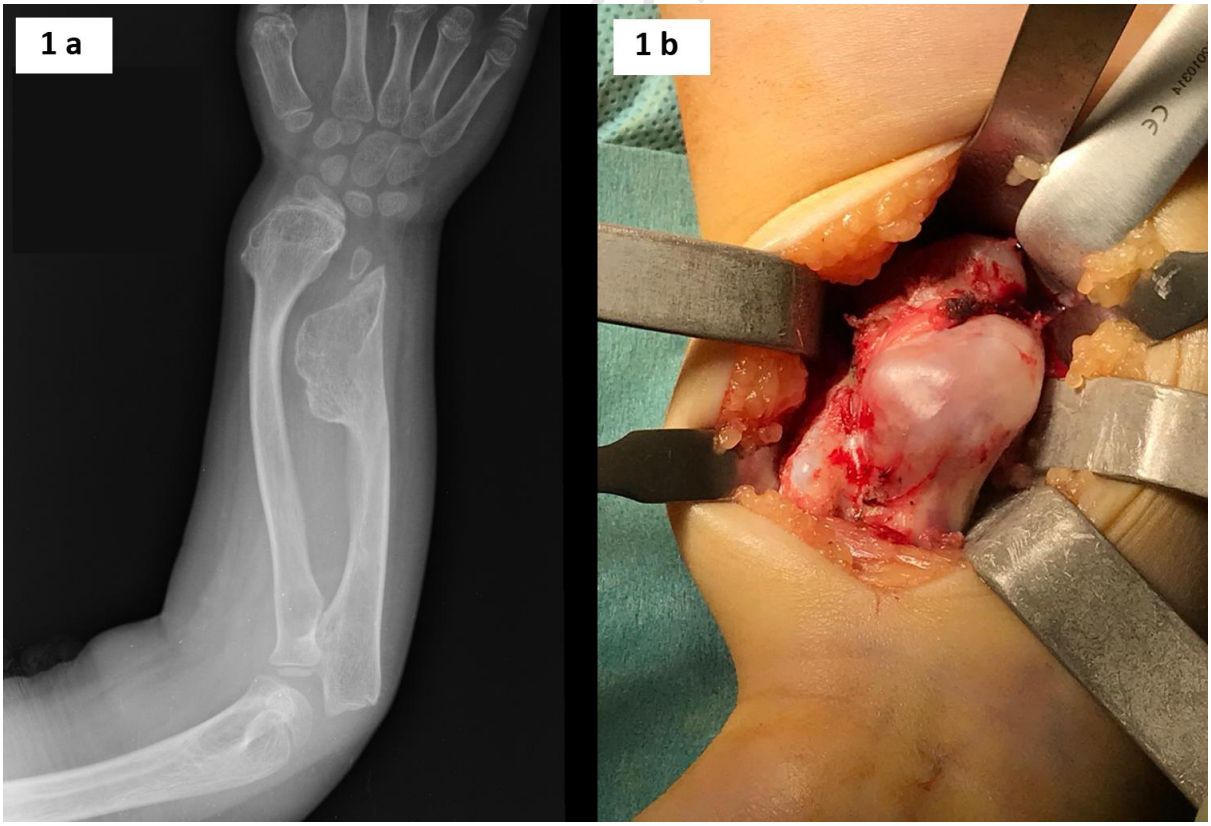
multiple osteochondromas, rare skeletal disease, natural history study, registry analysis, pediatrics, patient management, cartilage, growth plates

1. INTRODUCTION

Multiple osteochondromas (MO, MIM#133700, #133701) is an autosomal dominant hereditary condition, characterized by the presence of two or more benign cartilage-capped bony outgrowths called osteochondromas [1]. Although a rare genetic disorder with a prevalence estimate of 1:50,000,[2] MO is among the most common inherited musculoskeletal diseases.

Osteochondromas arise from the perichondrium of long bones and the surface of flat bones,[3,4] and are rarely present at birth **Figure 1**. Osteochondromas can be confused with an enchondroma, also derived from the actively proliferating cartilaginous tissue but grows as an intraosseous chondroma. [5]

Figure 1a. Anteroposterior radiographic evaluation of an Osteochondromas. Figure 1b. The same osteochondroma during surgical excision



As pathogenicity of osteochondromas is linked to active growth plates, proliferation and growth occurs from early childhood to growth plate closure.[3,6,7] A key complication is the malignant transformation of osteochondromas into a secondary peripheral chondrosarcoma during adulthood. In 70–95% of patients, MO occurs as a result of mutations in the *exostosin-1* (*EXT1*) and *exostosin-2* (*EXT2*) genes, which encode exostosins – transmembrane glycosyltransferases involved in the biosynthesis and elongation of heparan sulfate chains.[8-13] In the minority of patients with MO who do not have these mutations, the underlying cause of osteochondroma formation is unknown.[3,14]

Due to the diversity in size, number, and anatomical location of osteochondromas, the clinical manifestations of MO are considerably heterogeneous. MO severity can be categorized using the Istituto Ortopedico Rizzoli (IOR) classification system, in which disease severity is split into three classes: I (mild), II (moderate) and III (severe).[15] MO-associated complications include deformities, limitations, decreased range of motion, bursitis, pain, vessel and nerve compression;[3,6,16] adult patients are frequently characterized by disproportionate short stature.[17,18]. To date no medical therapy is available to prevent the formation of osteochondromas,[19,20] and palliative management of symptoms is used for mild MO. For more severe MO, excisions are the primary treatment, but should be avoided if possible due to a risk of pain exacerbation.[21] Additionally, although MO excisions conducted in pediatric patients have often been reported to have beneficial effects, there is a risk that these procedures may lead to a variety of problems including neurologic complications, risk of fracture, compartment syndrome and arterial laceration. [49]

To date, most clinical and genotype-phenotype studies of MO have been cross-sectional. These studies have contributed to our understanding of the anatomic burden of MO.[22-26] However, they have offered limited insight into disease development during childhood and adolescence when MO is most active. Thus, we performed an analysis of longitudinal registry data from an Italian cohort of pediatric patients with MO, focusing on clinical indices of disease severity and evolution, and surgeries. MO was considered to evolve when changes in disease severity class (defined using a

validated IOR classification scheme)[15] were recorded over time. The objective of this study was to assess and describe the natural history of MO according to meaningful clinical features and to examine the resulting symptom management burden.

2. METHODS

2.1. Participants and Setting

This study analyzed data from the Registry of Multiple Osteochondromas (REM; NCT04133285), collected between 2003 and 2017. [27] The REM is a standardized patient registry managed and updated by the Department of Rare Skeletal Disorders (DRSD) and Clinical Bioinformatics Laboratory (CLIBI) staff of the IOR in Bologna, Italy. The REM is a repository of clinical, genetic, surgical, and genealogical details of pediatric and adult patients with MO, accessible via a web-accessible platform that complies with current privacy requirements and medical informatics standards. The REM includes both prospectively and retrospectively captured data on pediatric and adult patients treated from 2003 to present at the outpatient clinic of DRSD who were evaluated for MO features and fulfilled clinical and radiological diagnostic criteria for MO. Collaboration with the Italian association of MO patients (ACAR Onlus) allows for continuous updates to the REM, providing a source of longitudinal clinical information.

Registry data used for the current analyses included patients ≤18 years of age with written informed consent (provided by parents or legal guardians) and at least one 12-month follow-up visit. The analyses included patient demographics, clinical features, surgeries and IOR classification.[15]

2.2. Data Collection

The clinical features assessed in this study included the presence and location of osteochondromas, deformities, functional limitations and IOR class. For patients who had undergone surgical procedures (either at the IOR or elsewhere) prior to their entry into the registry, relevant data were collected via patient narrative reports, supported by medical documentation. All surgical procedures during the

follow up period were performed by five different surgeons of the Ward of Pediatric Orthopedics and Traumatology at IOR.

The number of osteochondromas was determined by physical examination and supported by imaging (radiography, magnetic resonance imaging [MRI], computed tomography [CT], and ultrasound). Multiple imaging techniques could be used per patient; choice of technique depended on the patient's age, location and size of their osteochondromas, and the experience of the treating clinician. Diagnoses were confirmed following clinical and radiological evaluations. The number of osteochondromas found in each patient were grouped across three ranges: ≤5, 6–20, and >20).[15,23]

Skeletal deformities and functional limitations were clinically and radiologically evaluated by IOR pediatric orthopedic surgeons. Since deformities are structural deviation of normal shape, size and/or alignment, the present study has considered the following impairments: genu valgum/varum, ankle valgus and forearm deformity. In addition, functional limitations were evaluated as the deviation from normal range of motion. [28]. Detailed assessment criteria are summarized in **Table 1**.

Table 1. Diagnostic criteria for skeletal deformities and functional limitations

Lower limb deformities[a]	**Criteria**
Leg-length discrepancy	Length differences >2.5 cm
Genu valgum	Intermalleolar gap >10.0 cm
Genu varum	Intercondylar distance >3.5 cm
Ankle valgus	Valgus >5.0 cm
Upper limb deformities[b]	**Criteria/definition**
Upper limb discrepancy	Humeral length differences >4.0 cm
Subluxation or luxation of the radial head	Possible dislocation of the radial head
Ulnar deformities	Madelung deformity
	Pseudo-Madelung deformity
	Forearm procurvation or bending
Functional limitations[c]	**Definition of normal range of motion**
Knee flexion/extension	Flexion-extension from 90° to 135°
Hip abduction	Abduction of 45°

Hip adduction	Adduction from 20° to 30°
Hip rotation	Intra-rotation and extra-rotation at 45° each
Elbow flexion/extension	Flexion-extension from 10° to 150°
Wrist and forearm rotation	Supination and prono-supination of 80/90° to 0° to 80/90°

[a]Defined according to literature [29-32] [b]Defined according literature [33,34] [c] Measured as deviations from the normal range of motion.[28]

MO severity was determined using a classification system in which the presence/absence of osteochondromas, skeletal deformities, and functional limitations is used to define three classes of disease severity, increasing from class I to III.[15] MO disease evolution was defined according to shifts across classes from Baseline to follow-up. These shifts were recorded only once for each patient. A shift to a higher class indicated disease progression, whereas a shift to a lower class indicated regression (III➔II, III➔I, II➔I).

Genetic evaluations were performed at the DRSD. Small variations in *EXT1/EXT2* exons, including the exon–intron boundaries, were assessed by denaturing high pressure liquid chromatography and direct sequencing; large rearrangements were assessed by multiple ligation-dependent probe amplification and/or quantitative polymerase chain reaction. The molecular analyses helped the diagnostic process at early disease stages in patients <3 years of age, when clinical diagnosis is a challenge.

1.1. **Statistical Analysis**

Patient data were analyzed from their first visit (Baseline) to the last follow-up visit. The incidence of MO-related events was assessed at 12, 24, and 36 months post-Baseline, which was considered appropriate for detecting disease evolution based on IOR multidisciplinary team experience. Missing data were not imputed. Patients were categorized into three groups based on age at Baseline corresponding to development stages of childhood (0–6 years), preadolescence (7–12 years) and adolescence (13–18 years). For analysis and descriptive purposes, patients were classified according to their Baseline age group. Patient height at Baseline and at the last follow-up visit was also

assessed. The z-score of patient height was calculated from the mean and standard deviation of the Italian pediatric population. [24,25]

Results were summarized with descriptive statistics. Continuous variables were described using median, mean, standard deviation, and 95% CI. Categorical data were summarized with patient numbers and percentages in each category.

The annual rates of emergence of new clinical features and occurrence of surgeries were calculated, as a non-stochastic value, overall and for each age group at 36 months of follow-up using the following formula:

$$\frac{12\frac{n}{N}x}{t}$$

Here, n=age group; N=overall; x=mean number of events per age group category; t=mean length of follow-up per age group category.

Estimates of the mean incidence rates of new osteochondromas, deformities, functional limitations, MO-related surgeries and disease evolution were calculated at follow-up Months 12, 24, and 36 using a Kaplan-Meier survival analysis. These were referred to as the incidence rates for the respective events. The difference in height z-score among the age groups was investigated using one-way analysis of variance (ANOVA) followed by the post-hoc pairwise Sidak test. Height z-scores of patients in each age group were compared with a healthy peer using the one sample t-test. The number of new osteochondromas within 12, 24 and 36 months of follow-up was strongly non-Gaussian with the Shapiro-Wilk test, so the relationship with age groups was assessed using the Kruskal-Wallis non-parametric test. The incidence of at least one clinical feature and disease evolution among groups was assessed using Pearson's chi-square test, evaluated by exact method. Statistical significance was set at a $P \leq .05$. All analyses were performed using SPSS v19.0 (IBM Corp, Armonk, NY, USA).

2. RESULTS

2.1. Patient Disposition and Demographic Data

Out of the 1,185 patients with MO whose data were available in the REM, 190 were eligible for inclusion; 158 had at least one follow-up visit and were included in this analysis. The remaining patients (N=995) were excluded due to age (adults: N=673), inadequate consent (N=121) or incomplete epidemiology data (N=201) (**Supplementary Figure 1**). Patient demographics are summarized in **Table 2**. The analysis set comprised slightly more males (55.1%) than females, and most patients (60.8%) were in the 0–6 years age group. The overall mean age was 6.2 years, with a mean follow-up of 55.8 months, ranging from 31.5 months for the oldest age group to 62.2 for the youngest group.

Table 2. Patient Baseline demographics

		Age group, years			
		0–6 (N=96)	**7–12 (N=41)**	**13–18 (N=21)**	**Overall (N=158)**
Age, years	Mean (SD)	3.2 (1.8)	9.1 (1.6)	14.1 (1.3)	6.2 (4.3)
	Median (min, max)	3 (0, 6)	9 (7, 12)	14 (13, 17)	5 (0, 17)
Gender, n (%)	Female	41 (42.7)	22 (53.7)	8 (38.1)	71 (44.9)
	Male	55 (57.3)	19 (46.3)	13 (61.9)	87 (55.1)
Inheritance, n (%)	Maternal	24 (25.0)	13 (31.7)	8 (38.1)	45 (28.5)
	Paternal	28 (29.2)	12 (29.3)	6 (28.6)	46 (29.1)
	De novo	43 (44.8)	16 (39.0)	5 (23.8)	64 (40.5)
	Not available (adopted)	1 (1.0)	0	2 (9.5)	3 (1.9)
Mutation type, n (%)	*EXT1*	59 (61.5)	21 (51.2)	11 (52.8)	91 (57.6)
	EXT2	19 (19.8)	13 (31.7)	4 (19.0)	36 (22.8)
	Negative	5 (5.2)	3 (7.3)	5 (23.8)	13 (8.2)
	Not available	13 (13.5)	4 (9.8)	1 (4.8)	18 (11.4)

EXT: exostosin gene; max: maximum; min: minimum; SD: standard deviation.

Family history of MO, available for 155 patients (98.1%), was split almost equally between maternal (29.0%) and paternal (29.7%) lineage. Of 140 patients with genetic assessments, 127 (90.7%) had *EXT1* or *EXT2* mutations; the remaining 9.3% were negative.

2.2. **Clinical Features: Osteochondromas, Deformities, and Functional Limitations**

2.2.1. Osteochondromas

At Baseline, 38.6% of patients presented with ≤5 osteochondromas and 48.7% presented with 6–20 osteochondromas (**Table 3**). The overall numerical range of osteochondromas was 0–27, with a median of 6. The 3 patients presenting with no osteochondromas were all in the youngest age group. In the 0–6 years age group, the mean number of osteochondromas per patient (7.4) was lower than that observed in the older age groups (8.7 for both groups).

Table 3. Clinical features at Baseline and follow-up

Osteochondromas					
		Age group, years			
		0–6 (N=96)	**7–12 (N=41)**	**13–18 (N=21)**	**Overall (N=158)**
Baseline					
With OCs	n (%)	91 (94.8)	36 (87.8)	20 (95.2)	147 (93.0)
With ≤5 OCs	n (%)	40 (41.7)	12 (29.3)	9 (42.9)	61 (38.6)
With 6–20 OCs	n (%)	47 (49.0)	21 (51.2)	9 (42.9)	77 (48.7)
With >20 OCs	n (%)	4 (4.2)	3 (7.3)	2 (9.5)	9 (5.7)
Without OCs	n (%)	3 (3.1)	0	0	3 (1.9)
Missing data	n (%)	2 (2.1)	5 (12.2)	1 (4.8)	8 (5.1)
Number of OCs	Mean (SD)	7.4 (6.0)	8.7 (6.4)	8.7 (6.6)	7.9 (6.1)
	Median (min, max)	6 (0, 27)	6.5 (1, 26)	6.5 (2, 23)	6 (0, 27)
At last follow-up					
With new OCs	n (%)	83 (86.5)	28 (68.3)	16 (76.2)	127 (80.4)
With no new OCs	n (%)	13 (13.5)	13 (31.7)	5 (23.8)	31 (19.6)
Without OCs	n (%)	0	0	0	0
Missing data	n (%)	0	0	0	0
Number of new OCs	Mean (SD)	5.3 (4.4)	5.0 (5.7)	4.5 (6.3)	5.1 (5.0)
	Median (min, max)	4.5 (0, 19)	3 (0, 21)	1.5 (0, 24)	4 (0, 24)
Annual rate of new OCs[a]	Year	0.60	0.35	0.28	0.49
Mean incidence					

rates: new OCs[a, b]					
Within 12 months	% (95% CI)	37 (27–47)	33 (18– 48)	25 (6–44)	34 (27–42)
Within 24 months	% (95% CI)	60.0 (50–70)	42 (26–58)	59 (36–82)	55 (47–63)
Within 36 months	% (95% CI)	70 (61–80)	66 (51–82)	75 (52–97)	70 (62–77)
At least one new OC[a]					
Within 12 months	n (%)	31 (32.3)	10 (24.4)	4 (19.0)	45 (28.5)
Within 24 months	n (%)	45 (46.9)	13 (31.7)	5 (23.8)	63 (39.9)
Within 36 months	n (%)	55 (57.3)	17 (41.5)	7 (33.3)	79 (50.0)
Deformities					
Baseline					
With deformities	n (%)	30 (31.3)	20 (48.8)	11 (52.4)	61 (38.6)
With ≥3 deformities	n (%)	11 (11.5)	7 (17.1)	3 (14.3)	22 (13.9)
Without deformities	n (%)	65 (67.7)	21 (51.2)	10 (47.6)	96 (60.8)
Missing data	n (%)	1 (1.0)	0	0	1 (0.6)
Number of deformities	Mean (SD)	0.3 (4.7)	0.5 (0.5)	0.5 (0.5)	0.4 (0.5)
	Median (min, max)	0 (0, 1)	0 (0, 1)	1 (0, 1)	0 (0, 1)
At last follow-up					
With new deformities	n (%)	60 (62.5)	24 (58.5)	7 (33.3)	91 (57.6)
With no new deformities	n (%)	13 (13.5)	10 (24.4)	6 (28.6)	29 (18.4)
Missing data	n (%)	23 (24.0)	7 (17.1)	8 (38.1)	38 (24.1)
Number of new deformities	Mean (SD)	2.1 (1.6)	1.6 (1.4)	0.8 (0.9)	1.8 (1.5)
	Median (min, max)	2 (0, 6)	2 (0, 5)	1 (0, 3)	2 (0, 6)
Annual rate of new deformities [a]	$Year^{-}$	0.07	0.08	0.02	0.06
Mean incidence rates: new deformities[a, b]					
Within 12 months	% (95% CI)	25 (15–35)	31 (15–47)	33 (6–59)	28 (19–36)
Within 24 months	% (95% CI)	44 (33–56)	44 (27–61)	51 (22–80)	45 (36–54)
Within 36 months	% (95% CI)	58 (46-70)	51 (33–68)	61 (32–90)	56 (47–65)
At least one new deformity[a]					
Within 12 months	n (%)	22 (22.9)	5 (12.2)	1(4.8)	28 (17.7)
Within 24 months	n (%)	30 (31.3)	8 (19.5)	3 (14.3)	41 (25.9)
Within 36 months	n (%)	35 (36.5)	13 (31.7)	3 (14.3)	51 (32.3)
Functional limitations					

Baseline					
With ≥1 functional limitation	n (%)	13 (13.5)	9 (22.0)	3 (14.3)	25 (15.8)
Without functional limitations	n (%)	81 (84.4)	32 (78.0)	18 (85.7)	131 (82.9)
Missing data	n (%)	2 (2.1)	0	0	2 (1.3)
Number of functional limitations	Mean (SD)	0.2 (0.4)	0.2 (0.4)	0.1 (0.4)	0.2 (0.4)
	Median (min, max)	0 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 1)
At last follow-up					
With new functional limitations	n (%)	23 (24.0)	10 (24.4)	4 (19.0)	37 (23.4)
With no new functional limitations	n (%)	11 (11.5)	6 (14.6)	3 (14.3)	20 (12.7)
Missing data	n (%)	62 (64.6)	25 (61.0)	14 (66.7)	101 (63.9)
Number of new limitations	Mean (SD)	1.3 (1.5)	1.1 (1.3)	0.9 (0.9)	1.2 (1.4)
	Median (min, max)	1 (0, 7)	1 (0, 5)	1 (0, 2)	1 (0, 7)
Annual rate of new limitations[1]	Year	0.01	0.00	0.01	0.01
Mean incidence rates: new limitations[a, b]					
Within 12 months	% (95% CI)	6 (0–15)	13 (0–29)	0 (0–0)	7 (0–14)
Within 24 months	% (95% CI)	27 (11–43)	13 (0–29)	38 (0–79)	23 (12–35)
Within 36 months	% (95% CI)	52 (32–71)	33 (9–56)	38 (0–79)	44 (30–59)
At least one new limitation[a]					
Within 12 months	n (%)	6 (6.3)	2 (4.9)	0	8 (5.1)
Within 24 months	n (%)	11 (11.5)	2 (4.9)	3 (14.3)	16 (10.1)
Within 36 months	n (%)	17 (17.7)	2 (4.9)	3 (14.3)	22 (13.9)

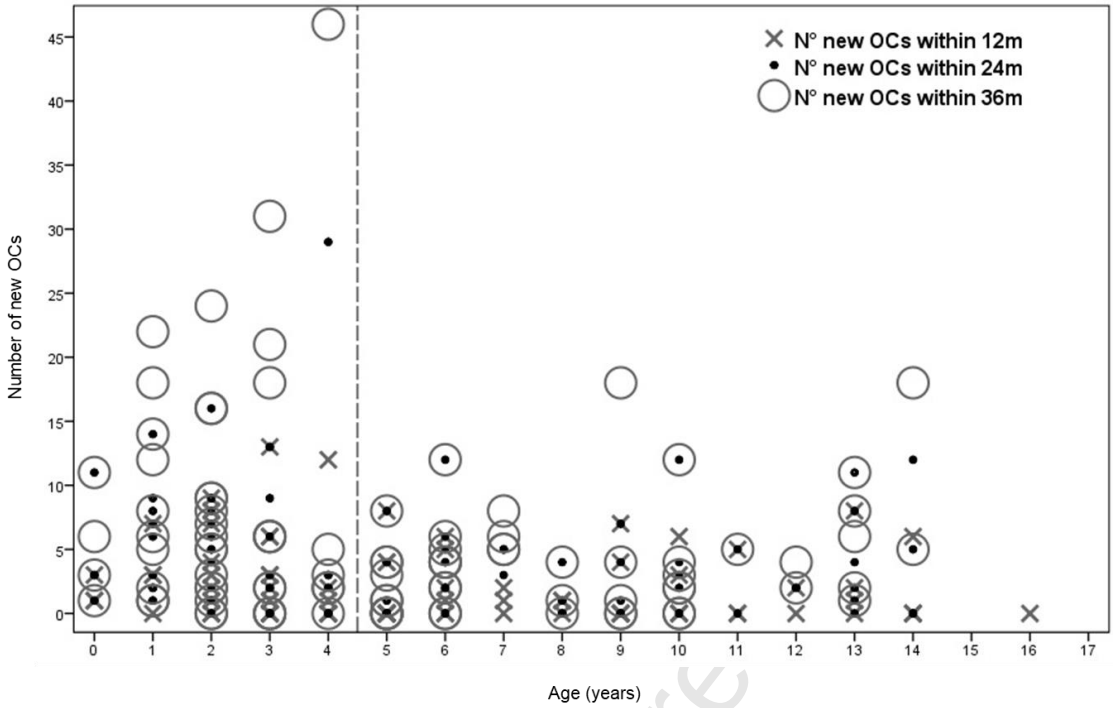
[a] Values cover the 36-month follow-up period; [b]The mean incidence rate is the Kaplan-Meier estimate of the proportion of patients with at least one new OC, deformity or functional limitation at the respective follow-up time. CI: confidence interval; max: maximum; min: minimum; OCs: osteochondromas; SD: standard deviation.

At follow-up, 127 patients (80.4%) had developed ≥1 new osteochondroma, with a mean count of 5.1 new osteochondromas per patient (**Table 3**). New osteochondromas totaled 813, ranging from 98 in the 13–18 years age group to 509 in the 0–6 years age group. The annual rate of new

osteochondromas was highest in the youngest patients, at 0.60 for the 0–6 years age group, 0.35 for the 7–12 years age group, and 0.28 for the 13–18 years age group.

The mean incidence rates of new osteochondromas were higher in the two younger age groups compared with the oldest age group (**Table 3**). Moreover, the peak of new osteochondromas development was detected in the younger age group; in particular, patients from 0–4 years underwent a higher number of new osteochondromas than the entire dataset within 12, 24 and 36 months of follow up (p=0.039, p=0.048, p=0.025, respectively; **Figure 2**). No significant differences arose when data were analyzed by gender (p=0.564). A Kaplan-Meier estimate of the mean incidence rate of new osteochondromas at 12 months of follow-up was 34% (95% CI, 27–42) which also increased with time (24 months: 55% [95% CI, 47–63]; 36 months: 70% [95% CI, 62–77]). Within 12 months, 29% of patients had developed ≥1 new osteochondroma, which increased with time: 40% at Month 24 and 50% by Month 36.

Figure 2. Distribution by age of new osteochondromas within 12, 24 and 36 months of follow up



M: month; OC: Osteochondroma.

2.2.2. Deformities

At Baseline, 61 out of 158 patients (38.6%) had deformities (frequently 1 or 2) with a mean (SD) number of 0.4 (0.5) (**Table 3**). Even if not statistically significant, limb deformities at Baseline were least prevalent in the 0–6 years age group (31.3%), compared with 48.8% and 52.4% of patients in the 7–12 and 13–18 years age groups, respectively.

At the last follow-up visit, 91 (57.6%) patients had ≥1 new deformity, the majority of whom (84 [92.3%]) were in the two younger groups (60 [65.9%] in the 0–6 years age group; 24 [26.4%] in the 7–12 years age group) ($p>0.005$) with annual rates of deformities of 0.07 (0–6 years age group), 0.08 (7–12 years age group) and 0.02 (1–18 years age group) at Month 36.

At Month 12, the Kaplan-Meier estimate for the mean incidence rate for new deformities was 28% (95% CI, 19–36), which increased to 45% (95% CI, 36–54) and to 56% (95% CI, 47–65) at Months 24 and 36, respectively.

The overall incidence of patients with ≥1 new deformity within 12 months was 17.7%, with incidences decreasing from the 0–6 years to 13–18 years age groups (22.9%, 12.2%, and 4.8% respectively) (p=0.023). While the overall incidence of new deformities increased within 24 and 36 months, the proportion of patients with deformities continued to be higher in younger versus older patients at both follow-up times.

2.2.3. Functional Limitations

Functional limitations were present in 15.8% of patients at Baseline (**Table 3**). By the last follow-up visit, new functional limitations had occurred in 37 patients (23.4%). Although the data are not statistically significant due to the small sample size, the mean overall number of new limitations was highest in the two youngest age groups (1.3 and 1.1 versus 0.9). Overall, functional limitations increased over time from 5.1% at 12 months to 13.9% at 36 months. However, this trend was driven primarily by increases in functional limitations from Month 12 to Month 36 in the 0–6 years age group.

2.3. **Surgical Procedures**

The overall incidence of MO-related surgical procedures prior to the Baseline visit was 11.4%, which increased from 5.2% in the 0–6 years age group to 42.9% in the 13–18 years age group (**Table 4**). Among 18 patients who had surgery, 16 (88.9%) were osteochondroma excisions. The mean number of surgical procedures also increased with age, from 1.2 to 2.4 procedures per patient for the 0–6 and 13–18 years age groups, respectively (p=0.012).

At the last follow-up visit, 44.3% of patients had undergone ≥1 new surgery. The mean number of surgical procedures was similar across age groups (2.4, 2.1 and 2.2, from youngest to oldest) with a maximum of 11 surgeries in one patient (occurring in the 0–6 years age group). Of note, the

proportion of patients with additional surgeries was higher in the two older age groups versus the younger age group; patients in the 7–12 years age group had notably more excisions and procedures to correct deformities than patients in other groups (**Table 4**). The mean number of surgical procedures increased with age within 12, 24 and 36 months (p=0.004; p>0.0005; p=0.002 respectively).

The Kaplan-Meier estimate of the mean overall incidence rate of surgeries at 12 months was 7% (95% CI, 3–12), which increased with the duration of follow-up (24 months: 17%, 95% CI, 11–23; 36 months: 28%, 95% CI, 20–36) (**Table 4**).

Surgical excisions were also assessed according to the anatomical location of the osteochondromas. Out of 90 excised osteochondromas, 50 (55.6%) were excised from lower limbs, 26 (28.9%) from upper limbs, and the remaining 14 (15.5%) from other regions, mainly scapulae and ribs.

Table 4. MO-related surgeries at Baseline and follow-up

		Age group, years			
		0–6 (N=96)	7–12 (N=41)	13–18 (N=21)	Overall (N=158)
Surgery prior to Baseline[a]					
All surgeries	n (%)	5 (5.2)	4 (9.8)	9 (42.9)[b]	18 (11.4)
Surgical excisions	n (%)	5 (5.2)	4 (9.8)	7 (33.3)[b]	16 (10.1)
To correct deformities	n (%)	1 (1.0)	1 (2.4)	4 (19.0)[b]	6 (3.8)
Missing surgical history	n (%)	0	0	0	0
Number of prior surgeries	Mean (SD)	1.2 (0.5)	2.0 (1.4)	2.4 (3.0)	1.9 (2.1)
	Median (min, max)	1 (1, 2)	1.5 (1, 4)	1 (1, 9)	1 (1, 9)
Surgeries at last follow-up					
With ≥1 new surgery	n (%)	37 (38.5)	23 (56.1)	10 (47.6)	70 (44.3)
Surgical excisions	n (%)	36 (37.5)	22 (53.7)	9 (42.9)	67 (42.4)
To correct deformities	n (%)	15 (15.6)	11 (26.8)	2 (9.5)	28 (17.7)
Missing surgical history	n (%)	0	0	0	0
Number of new surgeries	Mean (SD)	2.4 (2.0)	2.1 (1.5)	2.2 (1.8)	2.2 (1. 8)
	Median (min, max)	2 (1, 11)	2 (1, 5)	2 (1, 6)	2 (1, 11)
Annual rate of new surgeries[c]	Year	0.01	0.05	0.03	0.02
Mean incidence rates[c]					
New surgeries within 12 months	% (95% CI)	2 (0–5)	16 (4–28)	17 (0–35)	7 (3–12)
New surgeries within 24 months	% (95% CI)	6 (1–11)	31 (16–47)	45 (20–70)	17 (11–23)
New surgeries within 36 months	% (95% CI)	18 (10–28)	45 (28–62)	45 (20–70)	28 (20–36)

[a]Patients may have had more than one surgical procedure; [b]Includes two patients who had a surgical procedure prior to the Baseline visit but no additional information was available; [c]Values cover the 36-month follow-up period. CI: confidence interval; max: maximum; min: minimum; OCs: osteochondromas; SD: standard deviation.

2.4. Evaluation of Height

Height measurements were available for 112 patients at Baseline (60 male, 52 female) and from 143 at the last follow-up visit (76 male, 67 female). The z-score evaluation highlighted a tendency for the younger MO population to be taller than healthy peers, while an inverted trend arose during puberty

until adulthood. In particular, the comparison of the median z-scores of the investigated patients versus median z-scores of Italian pediatric population showed that younger patients have higher scores (p=0.001), patients aged 6–13 years are comparable with the Italian population (p=0.965), while all median z-scores of patients >13 years shifted to lower values (p<0.0005). (**Supplementary Figure 2A**). This trend was not significantly affected by gender (p=0.395). In addition, grouping the data according to age demonstrated that 13 years is the cut off point for stature; at 13 years of age, MO patients start to be averagely lower than peers (P<0.0005) (**Supplementary Figure 2B**).

2.5. **Disease Evolution**

Table 5 summarizes the distribution of MO severity at Baseline across age groups and the evolution from Baseline to last follow-up visit. Most patients (58.9%) had class I disease, followed by class II (25.3%) and class III (15.8%). At last follow-up, the proportion of patients with more severe MO increased: most had either class II (75 of 158 patients, 47.5%) or class III (46 patients, 29.1%); 37 patients (23.4%) had class I.

After the follow-up period (mean follow-up 55.8 months, SD 36.8) an equal proportion of patients (46.2%) exhibited either no progression or progression to more severe disease. Among patients whose disorder progressed (73/158 patients, 46.2%), most (41/73 patients, 56.2%) transitioned from class I to class II, 31 (out of 41 patients, 75.6%) of whom were in the 0–6 years age group. A similar proportion progressed from class II to III (14/73 patients [19.2%], mostly in ≥7 years age groups) and from class I to III (18/73 patients [24.7%], 16/18 from the 0–6 years age group) (p=0.005). As age increased from the 0–6 to 13–18 years age group, disease progression decreased (p=0.007). Regression occurred in the remaining 12 out of 158 patients (7.6%; 10 patients IOR class III➔II, 1 patient III➔I, 1 patient II➔I). The regression of 7 patients was related to surgical procedures, whilst the remaining 5 had a spontaneous rebalance of impairments.

Kaplan-Meier estimates of the mean incidence rates for disease evolution from Baseline to 12, 24, and 36 months of follow-up were 14% (95% CI, 8–19), 28% (95% CI, 21–36), and 42% (95% CI, 33–50) (**Table 5**).

Table 5. Disease evolution from Baseline to last follow-up

		Age group, years			
		0–6 (N=96)	7–12 (N=41)	13–18 (N=21)	Overall (N=158)
Disease stage at Baseline visit					
Class I[a]	n (%)	66 (68.8)	18 (43.9)	9 (42.9)	93 (58.9)
Class II[a]	n (%)	17 (17.7)	14 (34.1)	9 (42.9)	40 (25.3)
Class III[a]	n (%)	13 (13.5)	9 (22.0)	3 (14.2)	25 (15.8)
Disease stage at last follow-up visit					
Class I	n (%)	20 (20.8)	7 (17.0)	10 (47.6)	37 (23.4)
Class II	n (%)	48 (50.0)	22 (53.7)	5 (23.8)	75 (47.5)
Class III	n (%)	28 (29.2)	12 (29.3)	6 (28.6)	46 (29.1)
Length of follow-up (months)	Mean (SD)	62.2 (38.9)	53.1 (33.5)	31.5 (19.7)	55.8 (36.8)
Progression at last follow-up visit	n (%)	53 (55.2)	17 (41.5)	3 (14.3)	73 (46.2)
Class I to II	n (%)	31 (32.3)	10 (24.4)	0	41 (25.9)
Class II to III	n (%)	6 (6.3)	5 (12.2)	3 (14.3)	14 (8.9)
Class I to III	n (%)	16 (16.7)	2 (4.9)	0	18 (11.4)
Regression	n (%)	7 (7.3)	4 (9.8)	1 (4.8)	12 (7.6)
No progression or regression	n (%)	36 (37.5)	20 (48.8)	17 (81.0)	73 (46.2)
Length of follow-up for patients with no progression or regression (months)	Mean (SD)	52.7 (38.8)	42.4 (33.9)	26.9 (18.6)	43.9 (34.9)
Mean incidence rates[b]					
Disease evolution within 12 months	% (95% CI)	12 (5–19)	21 (8–34)	6 (0–18)	14 (8–19)
Disease evolution within 24 months	% (95% CI)	30 (20–40)	28 (13–42)	20 (0–40)	28 (21–36)
Disease evolution within 36 months	% (95% CI)	46 (35–57)	41 (24–57)	20 (0–40)	42 (33–50)

[a]The IOR severity class based on the presence or absence of deformities and/or functional limitations;
[b]Values cover the 36-month follow-up period. CI: confidence interval; OCs: osteochondromas; SD: standard deviation.

3. DISCUSSION

This retrospective registry analysis of Italian pediatric patients with MO investigated key clinical features and natural history of the disorder. MO is characterized by continuous progression during childhood. At skeletal maturity, the growth and related clinical signs of osteochondromas slow or stop, after which different manifestations of the disorder, such as arthritis and/or peripheral chondrosarcoma transformation, arise.[6,37] Currently, no published literature provides a longitudinal overview of the disease features, impairments and evolution in MO patients.

With the exception of family history data, for which previous studies have shown considerable variation,[2,38,39] our data on demographic distribution and genetic background are consistent with the literature,[2,38,40] suggesting that the analyzed dataset is representative of the worldwide MO population.

Previous studies have established that the number of osteochondromas represents an important predictor of disease severity in patients with MO, showing that more lesions lead to more impairment.[25,41] Although our results show a lower average number of osteochondromas at Baseline compared with other studies (possibly reflecting the higher proportion of younger children in our analysis,)[22,25] there was a clear increase in numbers of osteochondromas and impairments at the follow-up visit. Almost a third of the patients developed new osteochondromas within 12 months, representing an overall risk probability estimate of 34%. Of note, the majority of patients who developed >5 osteochondromas within a mean follow-up period of 4.8 years were in the group aged 0–6 years. Together with the increased rate of new deformities in the youngest group, these results support the importance of frequent disease monitoring during childhood, especially for younger patients. A better understanding of individual disease progression would improve patient management through timely scheduling of surgical procedures, early interventions, and determination of the appropriate time-intervals to leave between imaging evaluations. Imaging evaluation can be stressful

for pediatric patients and increases exposure to radiation; minimizing the frequency of these procedures could be beneficial.[42,43]

Due to missing data, our results on functional limitations should be interpreted with caution. However, the data again suggest increased presence of new functional limitations at each follow-up visit, and a higher incidence in young children. Despite this, given the rates of new osteochondromas and deformities recorded in this study, it was expected that higher rates of functional limitations would be found. These relatively low functional limitation rates may be attributable to excision of osteochondromas and/or surgical procedures performed to prevent and treat impairments; this is supported by the high number of patients with no disease progression and/or regression, the higher incidence of prior surgeries in the 13–18 years age group at Baseline, and the greater proportion of patients in the older age groups (≥7 years) undergoing surgery over 1 year of follow-up versus the youngest age group. A well-known controversy exists concerning the timing of surgical intervention.[44] Some authors recommend surgery in younger patients, while bone remodeling is still occurring,[45] whereas others recommend postponing surgical procedures to preadolescence/adolescence, when rapid growth takes place [46,47] based on evidence from long-term follow-up studies showing recurrence in children undergoing surgery too early.[34,48]
The current evaluation of stature is in accordance with previous studies in patients with MO.[17,18] Our data show that during pre-adolescence/adolescence, height increases slowed, meaning that a large proportion of patients with MO are shorter than their unaffected peers when they reach adulthood. One explanation for this is that altered heparan-sulfates lead to earlier growth plate maturation in adolescents, resulting in an advancement in skeletal age relative to their chronological age.[18] This is likely to be connected to puberty and the related changes that can affect skeletal development.

Earlier epiphyseal closure also affects MO disease evolution.[18] Whereas most patients in the 0–6 and 7–12 years age groups clearly showed disease evolution, older patients had comparatively stable

disease. Conversely, disease regression was observed in 12 patients during follow-up; this may possibly have been related to surgical correction and/or a natural rebalance of impairments during skeletal growth.

The key limitations of this study are related to the fact that it was retrospective, restricting the availability of data and types of analysis that could be conducted; for example, the number of patients within each age group differed, limiting the robustness of the comparison between groups. Additionally, in the analysis of deformities, osteochondromas and functional limitations, the current study only considered the number of events that occurred over time, not taking other characteristics such as type/extent of functional limitation or size of osteochondroma into account. Finally, a longer period of follow-up (e.g. 5 years) could have allowed for further relevant information on the evolution of multiple osteochondromas to be obtained.

4. CONCLUSIONS

Characterizing the epidemiology and the natural history of MO in this representative pediatric population provides valuable, clinically-relevant insight for the design of the first interventional study, (NCT03442985) evaluating the efficacy of the retinoid acid receptor agonist, palovarotene, in preventing new osteochondroma formation and disease evolution in pediatric MO. In additional to enabling clinical trial evaluation, these findings have crucial implications for patients during childhood to inform physicians on the implementation of treatment strategies to prevent the onset of impairments as these patients progress into adulthood.

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5.6. **Data sharing statement:** Individual participant data that underlie the results reported (text, tables, figures, and appendices) during this study are available following deidentification, for any scientific purpose upon reasonable request. In addition, study

protocol and informed consent forms are available. Proposals for data access, approved by an independent review committee, should be submitted beginning 3 months and ending 5 years following article publication to luca.sangiorgi@ior.it. To gain access, requestors will need to sign a data access agreement.

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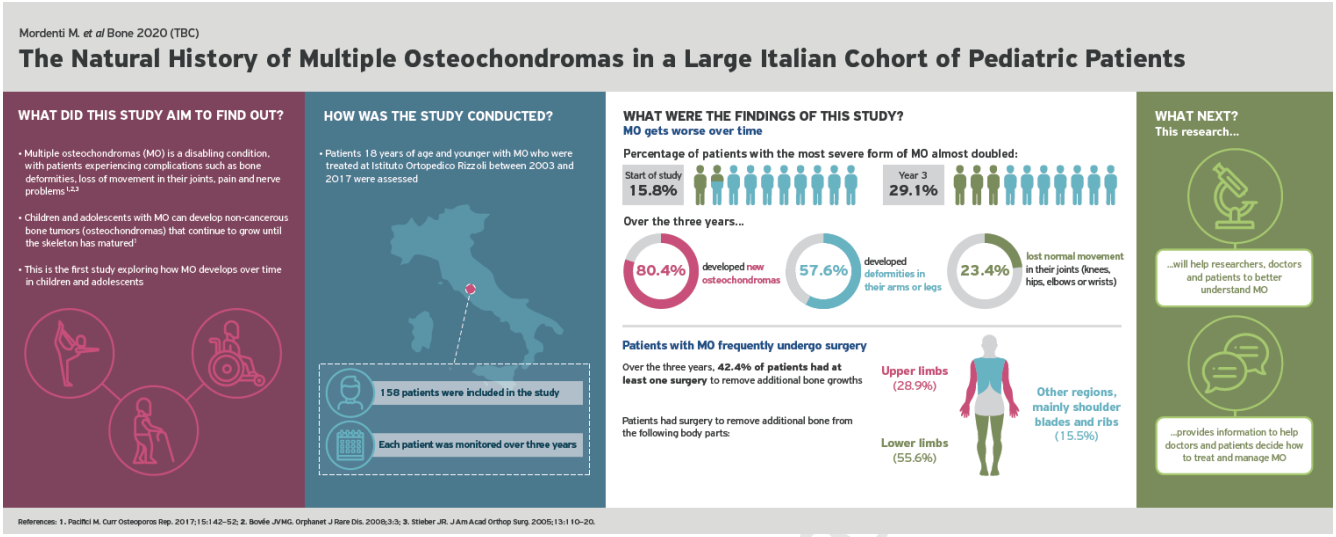
Credit author statement:

MM, MB, FS, LS: Conceptualization; **MM, MB, EP, MG, DA, MT, FS, LS:** Methodology; **MM, MB, DA, FS:** Formal Analysis; **MM, MB, EP, MG, DA, MT, FS, LS:** Investigation; **MM, MB, DA, FS, LS:** Writing - Original Draft; **MM, MB, EP, MG, DA, MT, FS, LS:** Writing - Review & Editing.

Graphical Abstract



HIGHLIGHTS

- Multiple osteochondromas (MO) is a rare hereditary skeletal disorder
- This study investigates MO natural history over 36 months in pediatric patients
- Incidences of new osteochondromas and deformities at Month 36 were 69.5% and 55.9%
- Disease evolution at Months 0, 24 and 36 was 13.7%, 28.1%, and 41.7%, respectively
- This study provides insight for patient management and therapeutic intervention