Osteochondromatosis: clinical variability and factors related to quality of life in children and adults

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ABSTRACT

Introduction. Hereditary osteochondromatosis is an uncommon, autosomal, dominant condition characterized by the presence of multiple bone growths.

Objective. To analyze factors associated with health-related quality of life (HRQoL) among children >2 years and adults receiving follow-up at a tertiary care children's hospital in Argentina.

Population and methods. Cross-sectional study of a follow-up cohort. HRQoL was measured using the Pediatric Quality of Life Inventory® (PedsQL) and the Short Form Health Survey (SF-36). Sex, age, sociodemographic characteristics, height, radiology, axis alteration and limb function, presence of pain, and malignant change were recorded. Severity was classified as per Pedrini et al. Parametric and non-parametric tests and regression analysis were done.

Results. A total of 66 cases (47 children and 19 adults) were included. Male/female ratio: 1.7/1. Median age: 13.4 years (r: 2.21-55.3). Pain was observed in 30/47 children and in 17/19 adults. Considering the adult bone age (or epiphyseal closure) as the cutoff point to define adult status, 11/37 children and 18/27 adults had a severe disease and 2/38 children and 9/27 adults had short stature. The average value of the physical component of HRQoL in children was 65.9 (SD: 22.5) and, in adults, 27.2 (IQR: 18.5-34.7). The presence of pain and clinical severity were significantly associated with a lower HRQoL, both in children and adults.

Conclusions. This study found that pain and disease severity had a negative effect on HRQoL.

Key words: *hereditary osteochondromatosis, pain, quality of life, rare diseases.*

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INTRODUCTION

Hereditary osteochondromatosis (HO) or hereditary multiple osteochondromas (HMO) is an uncommon, autosomal, dominant condition characterized by the presence of multiple bone growths, frequently located in the metaphyses.[1-3] The estimated prevalence of HO is 1:50 000. Tumor suppressor genes *EXT1* (OMIM 133700) and *EXT2* (OMIM 133701) are involved,[4,5] and approximately 10% were described as *de novo* mutations. This condition is associated with skeletal and extraskeletal complications, including limb-length discrepancy, bone deformities, short stature, pain, and vascular, peripheral nerve, and spinal cord compression. The most severe complication is the malignant transformation of osteochondroma. Recent studies have estimated that the risk for malignant change is approximately 2%.[6,7]

Since the first clinical description by Gockelius et al., in 1740, major improvements have been made in terms of surgical recommendations and techniques for skeletal deformities. However, in recent decades, the care of children with chronic conditions has shifted, and now the emphasis is not exclusively focused on orthopedic care and rehabilitation, but also on an improved general well-being.[8,9]

A historical and epidemiological study was conducted in our department to review the medical records of a retrospective cohort of 45 patients diagnosed with HO; 52% of them referred pain at some point

during follow-up.[10] Although chronic pain has a negative effect on the quality of life, we have found only few international studies about quality of life and pain in children with HO, and no national study.[11-16]

Health-related quality of life (HRQoL) is a multidimensional construct that attempts to measure the impact of disease on the quality of life of people based on their own perspective. In Argentina, HRQoL can be measured using the local validated version of generic instruments like the Pediatric Quality of Life Inventory (PedsQL) –useful in children and adolescents– and the Short Form Health Survey (Sf-36) –for the adult population.[17,18] Both instruments have been broadly used in our country and worldwide to analyze different diseases.

Our objectives were to analyze HRQoL in patients aged 2 years and older who were diagnosed with HO, who have received care and/or follow-up at our hospital since January 1998, and to analyze the eventual association between quality of life and skeletal and extraskeletal complications and clinical severity.

POPULATION AND METHODS

This was an observational, cross-sectional study of a cohort of patients with clinical and radiological diagnosis of HO seen for the first time and/or during follow-up at the skeletal dysplasia clinic of our hospital. All patients older than 2 years registered in the database as of 1998 were considered eligible. Cases with other medical conditions that may have impacted their quality of life and those who did not agree to participate in the study were excluded.

After a pilot test, a trained observer (RA) administered the HRQoL and pain surveys, registered demographic variables, and conducted a physical examination based on pubertal development and clinical severity, according to Pedrini et al.[19,20]

The anthropometric assessment included weight, height, and head circumference. The following demographic variables were recorded: place of residence, ethnicity, unmet basic needs (UBNs), and level of education of children and their parents. Other expert observer (VF) analyzed full body X-rays.

Other variables obtained by reviewing the medical records and validated during history taking included age at the time of the first consultation, number of prior surgeries, skeletal complications, e.g., pneumothorax, hemothorax, peripheral nerve compression, paresis, malignant change.

HRQoL was assessed using the PedsQL® questionnaire, version 4.0, for children and adolescents aged 2-18 years, and the SF-36 questionnaire for adults older than 18 years.[17,21] The PedsQL is made up of 23 items that assess physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). It asks questions regarding the past month using a Likert scale scoring from 0 to 4, where 0 means "It was never a problem" and 4, "It was always a problem". There are 7 versions of the questionnaire: 4 are completed by parents or caregivers (2-4 years old, 5-7 years old, 8-12 years old, 13-18 years old) and 3 are completed by children (5-7 years old, 8-12 years old, 13-18 years old). The PedsQL is self-administered by children aged 8-18 years and by the parents of children aged 2-18 years. For children between 5 and 7 years old, the questionnaire is read during the interview. For the analysis of results, the 0-4 scale undergoes a linear transformation into a 0-100 scale; the average of individual answers is estimated in a range from 0 (worst) to 100 (best).

The SF-36 is made up of 36 items and assesses 8 domains: physical functioning, limitation due to a physical problem, body pain, social functioning or role, mental health, limitation due to emotional problems, vitality, and overall health perception. These 8 domains are grouped into a physical and a mental component. The score for each domain ranges from 0 to 100 (100 means optimal health and 0, a very poor health).

Pain was assessed with a survey designed and used by the hospital's Department of Palliative Care. There are 2 survey versions: for children aged 5-7 years and for children older than 7 years. The surveys referred to the past month and included the following variables: presence or absence of pain, severity (Faces Pain Scale-Revised, FPS-R),[22] site, characteristics (somatic or neuropathic pain), pain frequency, and treatment.

Clinical severity was defined according to Pedrini et al.,[20] and classified into 3 groups based on the presence of deformities (shortening of long bones, bowing, scoliosis, genu valgum or genu varum, ankle deformity) and functional limitations:

- Group I: no deformity and no functional limitation (A ≤ 5 sites of osteochondroma; B > 5 sites of osteochondroma).
- Group II: deformity without functional limitation (A ≤ 5 sites with deformity;

B > 5 sites with deformity).
- Group III: deformity and functional limitation (A functional limitation in 1 site; B in more than 1 site).

Bias control

The information bias was controlled by creating an intimate environment for interviews and warranting answer confidentiality as well as giving the necessary time to complete them.

Statistical analysis

Data were entered in a database and the statistical analysis was performed using the Statistix 8.0® software. Descriptive statistics were used for categorical and continuous variables. In children aged 8.0 and 18.9 years, the difference between children's and caregivers' answers was analyzed using the Wilcoxon test. A univariate analysis of HRQoL and the variables age, sex, maternal level of education, UBNs, presence of pain, clinical severity, and prior surgeries was done. The variables that showed a significant association were analyzed with a multiple regression to assess which ones better predicted the quality of life score.

In adults, the SF-36 questionnaire was analyzed using the SPSS® software. A univariate analysis of HRQoL and the variables age, sex, place of residence, met basic needs (MBNs), clinical severity, short stature, pain, pain severity, and prior surgeries. The general statistical significance was established at $p < 0.05$.

Ethical aspects

This study was approved by the hospital's Department of Teaching, Research, and Ethics. All participants and/or their parents signed a consent. Data were dissociated to maintain confidentiality as per the personal data protection law.

RESULTS

Out of 91 cases receiving follow-up at the Department, 66 met the inclusion criteria; 71.2% were children (n = 47) and 28.8%, adults (n = 19). Participant's median age was 13.4 years (range [r]: 2.2 and 55.3); 39 were males (59.1%). *Table 1* describes the sample characteristics. The median age at the onset of the first symptom was 2 years (r: 0-9) in children and 6 years (r: 0.8-30.0) in adults; the most frequent initial site was the knees. The peripheral skeleton was affected the most; the knees, proximal humeri, hands, and hips were the most common sites. The site was the cervical spine in 5 patients and 1 child required surgery due to medullary compression. Considering the adult bone age (or epiphyseal closure) as the cutoff point to define adult status, 29.7% (11/37) children and 66% (18/27) adults had a severe disease. It was not possible to classify clinical severity in 1 child and 1 adult. Also, 2/38 children and 9/27 adults classified based on bone age had short stature.

Surgery was required by 53.7% of patients, an average of 2.8 surgeries per case (r: 1-11). The median age at the time of the first surgery was 8.85 years (r: 3.5-21). Complications included paresthesias (15/66), paresis (2/66), spontaneous bruising (1/66). In our sample, no malignant transformation was observed.

PEDsQL 4.0

The overall quality of life reported by children

TABLE 1. *Sample characteristics (n = 66)*

Sex (M:F)	1.7:1
Cases in the family	43/15 families
Age (years), median (range)	13.4 (r: 2.2-55.3)
Place of residence n (%)	
Buenos Aires	81.8
Other provinces	18.2
Health insurance (%)	55.4
UBNs (%)	40.6
Level of education (%)	
School-aged child attending school (n = 38)	100
Complete secondary or higher education, adults (n = 26)	76.9
ID and/or learning disorders	7.8

UBNs: unmet basic needs. ID: intellectual disability.

was 72.6% (SD 14.2), whereas that reported by their caregivers, 73.17% (SD 17.8). According to children, the school domain was the most affected area, whereas caregivers referred to the emotional aspect. No statistically significant differences were observed between children and their caregivers in any aspect (*Table 2*).

The single-factor analysis showed that the score for the physical component of quality of life was 17.1 points lower in the group of females ($p = 0.003$); 21.9 in the clinical severity III group ($p = 0.03$); 18.7 in children who referred pain in the past month ($p = 0.009$); and 12.5 in children whose mothers' level of education was primary or incomplete primary education ($p = 0.04$). No statistically significant differences were observed in terms of age, UBNs, short stature, presence of affected family member or prior surgeries (*Table 3*).

Using a multiple regression model, HRQoL was significantly adjusted in children with clinical severity III (limb deformity and functional limitation) and presence of pain.

SF-36

Table 4 summarizes the results of the SF-36 questionnaire. The total physical component was 19.3 points lower than the emotional component. Among female patients, the physical and social function was lower than among males, whereas the latter showed a lower physical role than females. In both groups, such difference was more than 5 points.

Table 5 shows the single-factor analysis. It was observed that the total physical component of quality of life was 17.3 points lower in the group with a worse clinical severity ($p = 0.001$) and 14.29 points in those with a worse pain severity ($p = 0.01$). Although no statistically significant differences were observed among the variables in relation to the total emotional component, it was observed that the score in the group who referred pain was 8.1 points lower than in the group without pain.

Pain

Pain in the past month was referred by 30/47 children and 17/19 adults. Pain affected the development of routine activities in 22/28 children and 10/16 adults. The most common type of pain mentioned was somatic pain, mostly referred to as "sharp pain." Pain severity varied: 35% said it was mild; 27.5%, moderate; and 37.5%, severe.

DISCUSSION

This is the first local study about HRQoL in children and adults with osteochondromatosis. The quality of life score for the physical domain was 18.3 and 17.3 points lower in children and adults with severe disease, respectively; 21.3 points lower in children with pain and 14.3 points lower in adults with severe pain.

The average quality of life score in children with severe clinical disease was similar to what has been described by Fano et al., in children

TABLE 2. *Score for children and parents across the different PedsQL domains*

Children's report (n = 34)	**Mean (SD)**
Physical functioning	72.61 (19.34)
Emotional functioning	73.24 (18.00)
Social functioning	76.03 (18.94)
School functioning	68.53 (20.61)
Psychosocial functioning	73.33 (15.12)
Total	72.60 (14.21)
Parent's report* (n = 34)	**Mean (SD)**
Physical functioning	75.52 (19.56)
Emotional functioning	68.62 (24.86)
Social functioning	78.83 (20.24)
School functioning	74.02 (20.22)
Psychosocial functioning	75.56 (19.94)
Total	73.17 (17.79)

*Wilcoxon test: not significant.
SD: standard deviation.

with osteogenesis imperfecta: 66.75 (SD: 22.9) and by Roizen et al. in children with chronic kidney disease: 67.17 (SD: 22.5).[23,18]

In addition, a high prevalence of chronic pain was observed in children and adults, in association with a worse quality of life. In this regard, Chhina et al., in a study about quality of life in 35 children and 57 adults with osteochondromatosis, described that the disease had a negative impact on quality of life.[13]

TABLE 3. *Univariate analysis of quality of life score in children*

Domains Variables (n)	Median for physical domain (IQR)	Median for psychosocial domain (IQR)	Median total (IQR)
Age			
8-12 years (21)	75.0 (62.5-82.8)	71.7 (54.9-80.8)	72.8 (61.4-77.2)
13-18 years (13)	78.1 (65.6-90.6)	81.7 (64.2-88.3)	77.2 (68.5-89.7)
Female sex (10)	62.5 (57.8-69.5)	71.7 (59.2-80.4)	70.1 (59.5-75.8)
Male sex (24)	79.6 (75.0-89.8)**	76.6 (61.7-87.9)	75.0 (63.9-88.9)
Level of maternal education			
Primary education or lower (21)	68.7 (62.5-79.7)	71.7 (58.3-81.7)	70.6 (61.9-76.1)
Secondary education or higher (10)	81.2 (67.2-96.9)***	77.5 (59.6-85.8)	77.2 (60.3-88.0)
UBNs (14)	71.9 (58.6-85.9)	75.8 (59.2-82.9)	71.2 (61.7-80.4)
MBNs (20)	78.1 (64.1-87.5)	73.3 (62.9-87.5)	75.0 (64.4-88.0)
Affected family member			
Yes (21)	78.1 (68.8-87.5)	78.3 (64.2-85.8)	75.0 (67.9-85.9)
No (13)	68.7 (51.6-85.9)	71.7 (52.5-83.3)	68.5 (53.3-83.2)
Place of residence			
Buenos Aires (30)	75.0 (62.5-85.2)	72.5 (61.3-81.7)	73.4 (62.8-78.3)
Other province (4)	85.9 (37.5-89.8)	87.5 (49.9-92.5)	87.5 (45.7-91.0)
Clinical severity			
I (9)	70.83 (5.9)	68.33 (13.6)	69.20 (4.5)
II (7)	87.94 (12.9)*	81.90 (9.9)	84.01 (5.1)
III (17)	65.99 (22.5)*	71.67 (16.8)	69.69 (3.3)
Pain yes (25)	68.8 (60.9-81.3)	71.6 (58.3-81.67)	71.7 (61.4-77.7)
Pain no (9)	87.5 (78.1-93.8)****	80.0 (67.5-91.7)	84.7 (72.8-90.8)*
Short stature			
Yes (3)	78.1 (34.3-87.5)	75.0 (47.5-87.1)	76.1 (39.4-86.7)
No (30)	76.6 (62.5-87.5)	72.5 (61.3-85.4)	74.5 (63.0-85.3)
Prior surgeries			
Yes (18)	79.7 (74.2-90.6)	71.7 (61.7-87.1)	75.0 (65.2-88.3)
No (16)	65.6 (60.2-80.5)	76.7 (57.5-81.7)	71.7 (61.4-77.7)

*ANOVA, Bonferroni test ($p = 0.03$); median test **($p = 0.003$), ***($p = 0.04$), ****($p = 0.009$).
IQR: interquartile range, UBNs: unmet basic needs, MBNs: met basic needs.

TABLE 4. *Health-related quality of life in adults (SF-36)*

	Mean osteochondromatosis (SD) (n = 17)
Physical functioning	64.12 (24.82)
Limitation due to a physical problem	58.82 (41.40)
Body pain	48.82 (25.56)
Social functioning	52.18 (17.69)
Mental health	56.47 (20.06)
Limitation due to emotional problems	63.24 (26.32)
Vitality	62.74 (43.91)
Overall health perception	65.41 (22.44)
Total physical component	32.86 (9.77)
Total emotional component	52.18 (12.97)

SD: standard deviation.

In our sample, pain had an effect on the development of routine activities in most children and two-thirds of adults, similar to what has been reported by Goud et al., who proposed that, in adults, pain was related to working place problems and, in children, to the perception of disease and school problems.[12]

Short stature showed similar values to what had been reported by Porter et al. and other authors; however, it did not evidence an impact on quality of life.[20,24-26]

This study allowed to better know the medical aspects and quality of life of children and adults with this rare condition so that adequate interventions considering emotional, involvement, and daily life activities interventions are carried out. The high prevalence of chronic pain and the impact on children's lives suggest the need for an early and comprehensive approach.

The limitations of this study are that only cases from a single tertiary care facility were included, where patients with a more severe condition are seen, and the small number of cases is not enough to analyze the statistical significance of certain variables related to quality of life.

This experience evidences the need for the early assessment of functional impact, severity, and pain to establish adequate therapeutic measures.

CONCLUSIONS

This study found that pain and disease severity had a negative effect on HRQoL. ■

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TABLE 5. *Univariate analysis of quality of life score in adults*

Component Variables (n)	Total median for physical component* (r)	Total mean for emotional component* (r)
Male sex (7)	29.16 (23.7-49.9)	54.66 (35.6-65.3)
Female sex (9)	29.71 (18.5-48.2)	55.41 (24.5-72.4)
UBNs (6)	36.81 (20.8-48.2)	55.42 (24.5-72.4)
MBNs (9)	29.16 (23.7-49.9)	55.4 (35.6-69.3)
Place of residence in Buenos Aires (12)	29.44 (18.5-49.9)	55.04 (24.5-72.4)
Place of residence in other province (4)	29.46 (23.7-69.3)	51.21 (37.4-69.3)
Clinical severity		
I (3)	44.5 (39.9-48.2)*	51.9 (45.1-56.7)
II (2)	39.8 (29.7-49.9)	55.0 (54.7-55.4)
III (11)	27.2 (18.5-34.7)*	51.7 (24.5-72.4)
Short stature (7)	28.76 (20.8-48.2)	55.79 (24.5-72.4)
Normal height (8)	29.76 (27.5-49.9)	55.03 (35.6-69.3)
Pain yes (14)	29.44 (18.5-49.9)	54.41 (24.5-72.4)
Pain no (2)	29.28 (28.8-29.8)	62.52 (55.8-69.3)
Pain severity		
Mild-moderate (6)	42.6 (31.8-49.9)	53.36 (37.37-65.27)
Severe (8)	28.31 (18.47-48.23)**	48.85 (24.50-72.37)
Surgeries		
Yes (12)	29.44 (23.7-49.9)	55.04 (24.5-69.3)
No (4)	27.77 (18.5-38.9)	55.19 (43.5-72.4)

*ANOVA, Bonferroni test ($p = 0.001$); **median test ($p = 0.01$).
UBNs: unmet basic needs, MBNs: met basic needs.

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